H.R. 1961—VIETNAM VETERANS AGENT ORANGE RELIEF ACT

HEARING

BEFORE THE

SUBCOMMITTEE ON
COMPENSATION, PENSION AND INSURANCE

OF THE

COMMITTEE ON VETERANS' AFFAIRS
HOUSE OF REPRESENTATIVES

NINETY-EIGHTH CONGRESS

FIRST SESSION

JULY 12, 1983

Printed for the use of the Committee on Veterans' Affairs

Serial No. 98-23

U.S. GOVERNMENT PRINTING OFFICE
27-768 O WASHINGTON : 1983

H761-5

COMMITTEE ON VETERANS' AFFAIRS

G. V. (SONNY) MONTGOMERY, Mississippi, *Chairman*

DON EDWARDS, California
BOB EDGAR, Pennsylvania
SAM B. HALL, Jr., Texas
DOUGLAS APPLEGATE, Ohio
MARVIN LEATH, Texas
RICHARD C. SHELBY, Alabama
DAN MICA, Florida
THOMAS A. DASCHLE, South Dakota
WAYNE DOWDY, Mississippi
MATTHEW G. MARTINEZ, California
LANE EVANS, Illinois
MARCY KAPTUR, Ohio
FRANK HARRISON, Pennsylvania
ALAN B. MOLLOHAN, West Virginia
TIMOTHY J. PENNY, Minnesota
HARLEY O. STAGGERS, Jr., West Virginia
J. ROY ROWLAND, Georgia
JIM SLATTERY, Kansas
JOHN BRYANT, Texas
BILL RICHARDSON, New Mexico

JOHN PAUL HAMMERSCHMIDT, Arkansas
CHALMERS P. WYLIE, Ohio
ELWOOD HILLIS, Indiana
GERALD B. H. SOLOMON, New York
BOB McEWEN, Ohio
CHRISTOPHER H. SMITH, New Jersey
DENNY SMITH, Oregon
PHIL GRAMM, Texas
DAN BURTON, Indiana
DON SUNDQUIST, Tennessee
MICHAEL BILIRAKIS, Florida
NANCY LEE JOHNSON, Connecticut

Mack Fleming, *Chief Counsel and Staff Director*

Subcommittee on Compensation, Pension and Insurance

DOUGLAS APPLEGATE, Ohio, *Chairman*

SAM B. HALL, Jr., Texas
THOMAS A. DASCHLE, South Dakota
MATTHEW G. MARTINEZ, California
G. V. MONTGOMERY, Mississippi
MARVIN LEATH, Texas
RICHARD C. SHELBY, Alabama
DAN MICA, Florida
WAYNE DOWDY, Mississippi

BOB McEWEN, Ohio
CHALMERS P. WYLIE, Ohio
JOHN PAUL HAMMERSCHMIDT, Arkansas
DENNY SMITH, Oregon
DAN BURTON, Indiana

CONTENTS

July 12, 1983

Page
H.R. 1961—Vietnam Veterans Agent Orange Relief Act 1

Opening Statements

Chairman Applegate 1
Hon. Bob McEwen 1
Hon. G. V. (Sonny) Montgomery 2

Witnesses

Anderson, Dr. Karl, Rockefeller University Hospital 59
Prepared statement of Dr. Anderson 200
Bederka, Dr. John, Department of Pathology, University of Illinois Medical Center
Prepared statement of Dr. Bederka
Beljan, Dr. J. R., senior vice president of Wright State University, Dayton, Ohio, representing the American Medical Association, accompanied by Leonard D. Fenninger, M.D., vice president for medical education and scientific policy, American Medical Association; and Harry N. Peterson, director of the division of legislative activities, American Medical Association 46
Prepared statement of Dr. Beljan 159
Chesney, Maj. Gen. Murphy A., Deputy Surgeon General, Department of the Air Force, accompanied by Col. George D. Lathrop, chief of the Epidemiology Division; Col. Patricia M. Moynahan, chief of the Occupational Epidemiology Section; and Dr. Joel E. Michalek, mathematical statistician, Data Sciences Division; all from the USAF School of Aerospace Medicine, Brooks Air Force Base, Tex.; and accompanied by Jack R. Spey, president, Ranch Hand Vietnam Association 17
Prepared statement of General Chesney 75
Davis, Sammy, Congressional Medal of Honor winner 34
Prepared statement of Mr. Davis 146
Enzinger, Dr. Franz, Department of Soft Tissue Pathology, Armed Forces Institute of Pathology 56
Prepared statement of Dr. Enzinger 167
Luster, Dr. Michael, scientist, National Institute of Environmental Health Sciences, National Institutes of Health 58
Prepared statement of Dr. Luster 172
Ratchford, Hon. William R., a Representative in Congress from the State of Connecticut 3
Prepared statement of Congressman Ratchford 70
Walters, Hon. Harry, Administrator, Veterans' Administration, accompanied by John Murphy, General Counsel; Donald Custis, M.D., Chief Medical Director; and Miss Dorothy Starbuck, Chief Benefits Director 7

Material Submitted for the Record

Letters:

U.S. Environmental Protection Agency to Chairman Montgomery re current uses of the herbicide 2,4,5-T 74

Medical reports:

Sammy Davis, Congressional Medal of Honor winner 150

Reports:

Page
"Health Effects of Agent Orange and Dioxin Contaminants," presented by William D. Dolan, M.D., chairman, Council on Scientific Affairs 163
"Immune Alterations," National Institute of Environmental Health Sciences 174
"Porphyria Cutanea Tarda," submitted by Dr. Karl E. Anderson, the Rockefeller University Hospital 200
"Dioxin-Associated Adverse Human Health Effects," submitted by Dr. John Bederka, Department of Pathology, University of Illinois Medical Center 206

Statement:

Panetta, Hon. Leon E., a Representative in Congress from the State of California, and chairman, Vietnam-era Veterans in Congress 67

Studies:

"Project Ranch Hand II," an epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides 82
Written committee questions and their response: Chairman Applegate to General Chesney 145

H.R. 1961—VIETNAM VETERANS AGENT ORANGE RELIEF ACT

TUESDAY, JULY 12, 1983

House of Representatives,
Subcommittee on Compensation,
Pension and Insurance,
Committee on Veterans' Affairs,
Washington, D.C.

The subcommittee met, pursuant to notice, at 8:35 a.m., in room 334, Cannon House Office Building, Hon. Douglas Applegate (chairman of the subcommittee) presiding.

Present: Representatives Applegate, Hall, Daschle, Montgomery, McEwen, Hammerschmidt, and Smith of Oregon.

Also present: Representative Bob Edgar, member of the full Committee on Veterans' Affairs.

OPENING STATEMENT OF CHAIRMAN APPLEGATE

Mr. Applegate. Good morning. The subcommittee will come to order. This morning we will continue our hearings on H.R. 1961, the Vietnam Veterans Agent Orange Relief Act.

We have had 2 days of hearings on April 26 and 27 on this proposal. Today we have the Veterans Administrator, Mr. Harry Walters, back with us. He made a brief appearance on April 26 and, as agreed, has returned in the event that there are additional questions for him.

A series of questions were submitted to the Veterans' Administration following our hearings in April and the responses were sent to each of the members of the subcommittee on June 29.

We will also hear from several professional and scientific witnesses and from the Office of the Surgeon General, the Department of the Air Force, as to their published Mortality Study on the Ranch Hand personnel.

At this time, I would like to recognize my colleague from Ohio and the ranking minority member of the subcommittee, Mr. McEwen.

OPENING STATEMENT OF HON. BOB McEWEN

Mr. McEwen. Thank you, Mr. Chairman. I would like to join with you and Chairman Montgomery and Representative Hammerschmidt in a welcome to our witnesses this morning. Hopefully, they will provide us with additional information upon which to form conclusions with respect to the subject before us.

As I stated on April 26 of this year, we are considering solutions to one of the most perplexing problems to confront the Congress and, indeed, the entire Nation. The controversy over the effects on veterans of agent orange will not go away and obviously it should not.

Obviously, as we approach consideration of legislation concerning it, we need to be as knowledgeable as possible. Many of the witnesses this morning are men of science and men of considerable stature in the medical world. What they have to say to us should be extremely helpful.

Mr. Chairman, I note that one of the witnesses is Dr. John Beljan, senior vice president of Wright State University in Dayton, Ohio. The doctor is representing the American Medical Association. He is from the Sixth Congressional District of Ohio, and I particularly wish to welcome him.

Mr. Chairman, back when we first started our hearings, I made a statement that I would like to repeat. It is that many of us in the Congress have an open and very inquisitive mind on this important issue. We wish to do that which is right. I also stated that when it's all over that it's my opinion that each of us on the subcommittee would make the best informed judgment that we could. That continues to be my position and I wish you Godspeed.

Mr. **Applegate**. Thank you, Mr. McEwen.

At this time I will recognize our very distinguished chairman of the full committee, Mr. Montgomery.

OPENING STATEMENT OF HON. G. V. (SONNY) MONTGOMERY, CHAIRMAN, FULL COMMITTEE ON VETERANS' AFFAIRS

Mr. **Montgomery**. Thank you, Mr. Chairman, and thank you for having these hearings. I look forward to being here this morning to hear from these different witnesses. I would like to welcome my colleague from Connecticut and I look forward to any remarks that he might have to say. Also, Mr. Chairman, I am quite interested in what the Ranch Hand Study might produce as well as other witnesses that we will hear from this morning.

We will have to take some action on this legislation in the near future, in my opinion. Thank you for giving me the opportunity to be a part of this subcommittee hearing.

Mr. **Applegate**. Thank you, Mr. Chairman. At this time I would like to recognize the very distinguished ranking minority Member from Arkansas, Mr. Hammerschmidt.

Mr. **Hammerschmidt**. Thank you very much, Mr. Chairman. I, too, want to commend you and Mr. McEwen for having these subcommittee hearings. I have no further comments at this time except to join you in welcoming these very distinguished witnesses we are getting ready to hear.

Thank you, Mr. Chairman.

Mr. **Applegate**. Thank you, Mr. Hammerschmidt. In addition to the very distinguished witnesses who are here to testify this morning, we are looking forward to hearing from our colleague, the Honorable Bill Ratchford of Connecticut. Later on in this morning's proceeding we hope to hear from our colleague from California, the Honorable Leon Panetta.

At this time, I would like to recognize Mr. Ratchford.

Mr. RATCHFORD. Thank you very much, Mr. Chairman and members of the subcommittee. You have a statement from me which I would like to be included in total in the record.

Mr. APPLEGATE. Without objection.

STATEMENT OF HON. WILLIAM R. RATCHFORD, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CONNECTICUT

Mr. RATCHFORD. I would applaud you for your continuing efforts in this area because this is a lingering problem which is not going to go away. About a year and a half ago, Representative Daschle and myself held an extensive hearing in the State of Connecticut on the problems of the Vietnam veteran generally and those relating to agent orange specifically. Frankly, in my 5 years in Congress I have not participated in a more graphic hearing or come away more compelled with the feeling that there was an unresolved problem facing Vietnam veterans and one that we, as Members of Congress, had not yet addressed.

The two Connecticut veterans hospitals have begun to perform the agent orange physicals. The one at Newington has performed 570 of these and in West Haven, 708. In fact, Connecticut has gone beyond a general response. We have through our legislature mandated the establishment of a Connecticut State Vietnam Herbicide Commission. That commission has now contracted for a statewide survey. While that survey is incomplete at this point, let me share with you the findings in the questionnaire response that has come back from 406 of the veterans who are affected by exposure to agent orange.

The figures are alarming, although not surprising. In that small population of 406 veterans and their families there are a total of 540 serious health problems—problems like cancer, neurological damage, miscarriages, multiple-birth defects, tumors, serious skin conditions, and unexplained illnesses.

Because of understaffing, the statistics on where and when these men served are still being compiled, but the medical findings compel a very close look.

The individual horror stories are even more graphic. One veteran, a crewmember of Operation Ranch Hand has had three children with multiple-birth defects since his service. One child was born without a collarbone and with a cleft palate. Another had a third breast, a club foot, and a cleft palate. The third died at birth of multiple-heart defects.

Another Ranch Hand crewmember had one healthy child. But one child was missing ears, eyelids, and had a cleft palate and a club foot.

There is no previous history of birth defects on either side of these veterans' families—I think I need to emphasize that.

Now most of the health problems that have surfaced in Connecticut, and I look forward with interest to the testimony of the Director, came from veterans who were ground troops in Vietnam. I know that we have had the benefit of the Ranch Hand Study within the past 2 weeks, but if I have a concern it is that it addresses itself to those who served in the Air Force, and not those who were the ground troops, who literally lived in the agent orange each and every day.

Two of the veterans in Connecticut who had served as ground troops had over 100 nonmalignant tumors removed from their bodies since returning from Vietnam. Think of it, 100 tumors removed from their bodies since returning from Vietnam.

Another veteran who was a constituent of mine kept a scrapbook, as did so many in Vietnam, and a list of the places he went and the times he was there. A check of his list against a list of the Ranch Hand spraying missions indicates that he was in several locations that were sprayed with agent orange. This particular constituent has developed serious liver problems and growths on the internal walls of his kidneys.

The plain and hard fact of the matter is, Mr. Chairman and members of the committee, that we are not keeping our commitment to the Vietnam veteran. It is not enough to send out a newsletter expressing concern. It is not enough for statements to be issued each and every Memorial Day or each and every Armistice Day on behalf of the Vietnam veteran.

The time is now for action and the action in question ought to be, in my judgment, moving forward with the legislation addressing itself to the problems of agent orange that you are now considering.

You know, I find veterans asking themselves, "If presumptive treatment, why not presumptive compensation?" And I find them asking also "If the citizens of Times Beach, exposed to dioxin at one-twentieth the level in agent orange, why not the citizens who served in Vietnam?"

Why am I asked this type question? Why are you asked this type of question? I know what my response is, it's one of embarrassment that I cannot provide a better answer on behalf of my country.

I am here today to testify on behalf of Connecticut men and women and their children who continue to suffer long after the end of the Vietnam War. Let the studies continue, by all means, but let there not just be studies. Let's not quibble over the smaller details. Dioxin is a killer and a crippler.

I know the VA Administrator has said that he opposes this legislation in part because it has, quote, "the potential for alarming millions of veterans and the population as a whole." Give us credit, Mr. Administrator, we are alarmed, but not only at the specter of dioxin, we are alarmed at the specter of an indifferent government which inflicts enormous suffering and is too callous to assume responsibility.

I strongly urge your support for this vital legislation. Thank you and I would be happy to respond to questions.

[The prepared statement of Congressman Ratchford appears on p. 70.]

Mr. Applegate. Thank you very much, Mr. Ratchford. We all know of your very intense interest and your involvement in this legislation and how much it means to you in your representation of your veterans, not just in your home State of Connecticut but throughout the United States. We sincerely appreciate your being here and expressing your ideas and views.

Mr. McEwen?

Mr. McEwen. I have no questions, Mr. Chairman.

Mr. Applegate. Mr. Montgomery?

Mr. Montgomery. I have no questions. I do appreciate the gentleman's strong testimony and he has shown a great interest in Connecticut. I assume from your statement that the two veterans hospitals in your State are doing what they can under the law and regulations that we have applied for examinations. Are you satisfied with the way those veterans hospitals are handling themselves?

Mr. Ratchford. Mr. Chairman, they have begun the examinations but there is very little as far as a course of treatment. So to examine is one thing, but to treat is something else. Mr. Daschle and I had the benefit of direct testimony and some of it, frankly, was such that it took your breath away.

We had one young couple come forward and the wife indicated that her husband had served in areas in Vietnam where agent orange was dropped. She said, "I want you to know that I went through a 10-month pregnancy. I delivered a child that was badly deformed and that child died after 21 days."

We then had another couple from my district come forward where the husband had served in Vietnam and they were recently married. The question they asked us was one that we could not respond to, and that is: "Since my husband served in this area, should we go ahead and have children?" That was the question they posed to us and that was the concern that they expressed since the male in question had been exposed to agent orange.

These are the tough questions that face us each and every day and until we are able to at least begin to provide answers to these questions, we have not kept our commitment.

Mr. Montgomery. Just one other question. You might have given it in your testimony and I might have missed it, do you have a percentage of deformities of the children of the veterans? Is it a higher percentage than just the veteran who is in the service? Have you had an opportunity for a survey such as that?

Mr. Ratchford. Chairman Montgomery, the survey which the State is conducting under its own Herbicide Commission set up by the 1982 session of the Connecticut General Assembly has not gone far enough for me to give you that type of data. As it comes in, I am more than willing to provide it to the committee.

Mr. Montgomery. Thank you.

Mr. Applegate. Thank you, Mr. Chairman. Mr. Hammerschmidt?

Mr. Hammerschmidt. No questions, Mr. Chairman.

Mr. Applegate. Mr. Daschle?

Mr. Daschle. Thank you very much, Mr. Chairman.

Bill, I think that was an excellent statement and, as usual, you very articulately represented the views of those veterans who attended that meeting and the meetings that you have had since that one. I share your conviction and I wish I could speak with the kind of eloquence that you have articulated again today.

Let me ask you: What do you think the view of the Vietnam veteran toward the Veterans' Administration is in Connecticut right now? Are they frustrated, are they just disappointed? When they go into a VA hospital, what concerns do they express to you?

Mr. **Ratchford**. Let me indicate that I think, Congressman Daschle, that attitudes have improved over the last year. I think the new Administrator who is about to testify is to be congratulated for his expression of concern about the Vietnam veterans and I find this attitude beginning to reach the veteran in Connecticut.

There still is a feeling, however, that those who are called upon in the veterans hospital to conduct the surveys have not been given the proper training so that they are sensitized to the unique problems medically facing the Vietnam veteran.

I know with time they can be addressed, but that is a current attitude and a concern that is out there.

Mr. **Daschle**. When they see a study like the so-called Ranch Hand study, which seemingly indicated no real difference between those who were exposed and those who were not, how do you think that contrasts or compares with the evidence that you have accumulated in your own district? What do you think when they see that kind of information?

Mr. **Ratchford**. Well, the type of response that I get from the Vietnam veteran is, "Why not us," and by "us" they mean the ground troops, "Why aren't they surveying us?" Now, of course, there is an ongoing survey and this committee was very responsible for moving that forward and we await those results. But I think until we have the results of the ground soldier who literally lived in the agent orange, who swam in it, who was required to breathe it day in and day out, unlike the Air Force person who could return at the end of the day to the base and shower it off. We have incomplete results, in my judgment.

Mr. **Daschle**. Well, I certainly share the view that you have expressed here and I want to thank you for a very good statement.

Mr. **Ratchford**. I thank the committee and I look forward to the testimony of the VA Director.

Thank you.

Mr. **Applegate**. Thank you very much, Bill.

The chairman, Mr. Montgomery, has asked that a letter from the Environmental Protection Agency, dated May 20, 1983, on the current annual usage of phenoxy herbicides 2,4,5-T be inserted into the record. Without objection, that will be done.

[The letter appears on p. 74.]

Mr. **Applegate**. I would say at this time that the Chair will invoke the 5-minute rule. We have a fairly long list of witnesses to appear before the committee. We want to give each the opportunity to be able to testify and give members adequate opportunity to pose questions. Therefore, we will invoke the 5-minute rule.

Our first witness today will be the Honorable Harry Walters, Administrator of Veterans' Affairs. Mr. Walters presented both an oral and a written statement at the hearing on April 26 and has made himself available at this time for any questions from any of the members. Along with him he has brought along some old friends, or should we say long-time friends who have worked with us and cooperated with us and we appreciate their presence here today.

At this time, Mr. Walters, do you have anything that you would like to add or to say before we allow the members to question you?

Mr. **Walters**. Yes, I do, Mr. Chairman.

STATEMENT OF HARRY WALTERS, ADMINISTRATOR, VETERANS' ADMINISTRATION, ACCOMPANIED BY JOHN MURPHY, GENERAL COUNSEL; DONALD CUSTIS, M.D., CHIEF MEDICAL DIRECTOR; AND MISS DOROTHY STARBUCK, CHIEF BENEFITS DIRECTOR

Mr. **Walters**. First of all, I would like to thank you personally for the courtesies extended to me by you and your staff. They are sincerely appreciated in light of the tight timetable that you had at the last subcommittee meeting and the tight timetable that you have today and that I have and your cooperation is appreciated very much.

As a principal advocate for America's veterans, all its veterans, I want to insure that they are treated with compassion, dignity, and respect and that they receive all the benefits they deserve and have earned as dictated by the laws of the land.

I have provided a written statement, as you have already stated, and I only wish to reiterate a few comments. First, our veterans deserve an answer on the agent orange issue. Therefore, I believe it to be critical that the integrity of the CDC study be maintained and that it proceed with all deliberate speed.

Second, I would like to reiterate the Veterans' Administration's commitment to maintain the integrity of our compensation package system. When the VA first briefed me on their recommendation for an agency position on H.R. 1961, they clearly opposed this legislation, primarily to protect the compensation systems for service-connected veterans.

I then asked the veterans' service organizations for their views on H.R. 1961 and found that both the DAV and the PVA opposed this legislation on the same general grounds as the agency. Mr. Chairman, the DAV and PVA are still opposed to this legislation. I chose to support their views and thus I developed the final VA position on this legislation. I still support their views on the integrity of our compensation package.

As I stated previously, it is evident that many of our veterans do not understand the benefits to which they are entitled and we in the VA are working to correct that deficiency. In this same vein, there are stories of how agent orange affects veterans and they are rampant. These stories are causing veterans to be sincerely concerned about their health and that of their offspring.

All in positions of public trust should do all we can to communicate the facts as they become known and I stress, Mr. Chairman the word "facts", so our veterans can react appropriately.

I am pleased to have Dorothy Starbuck, and Dr. Donald Custis, and John Murphy with me to assist in responding to the subcommittee's questions.

Thank you.

Mr. **Applegate**. Thank you, Mr. Walters. At this time, I would like to recognize my colleague and the ranking minority member from Ohio, Mr. McEwen.

Mr. **McEwen**. Thank you, Mr. Chairman. Mr. Walters, I, too, join in welcoming you to the committee today, and wish to take a brief moment to express my appreciation for the compassion and concern that you have shown for America's veterans since assuming your position as Administrator.

During our difficult hearings in April, as we began to look into this issue in depth, you were generous enough to stop by and share briefly with the committee, the interests of the Veterans' Administration on this issue, which helped set the parameters for our discussion and for our hearing on that day. You did that under the constraints of other obligations and responsibilities throughout the course of the day and thereby subjected yourself to comments that "You were testifying and running," so to speak. You were willing to do that regardless of what the comments would be from those who heard your testimony and I wish to commend you for doing that because your brief testimony was most helpful on that day.

In the interim, you and the administration have been most cooperative and helpful in our search here and I thank you for taking the time to appear here along with your staff and for the opportunity to study the substantial testimony that you have submitted.

It has been stated that Veterans' Administration doctors are hidebound on this issue in that they just refuse to concede the possibility that cancer or other serious disabilities can result from exposure to agent orange.

Could you comment on that and do you sense an attitude problem among VA doctors around the country?

Mr. **Walters**. Mr. McEwen, when I first took over as Administrator of the VA, I took 5 hours of my time and went down and had dinner with the former Administrator Max Cleland in Georgia and he counseled me about agent orange. He was concerned that the Veterans' Administration, and perhaps some of the doctors and employees that worked for it, were not as sensitive to the issue of agent orange as he might have wished when he was Administrator. I share that with you today and I am sure that Administrator Cleland would share it with you if he were here.

Since I have been Administrator, I might add, I have sent out video tapes, I have visited hospitals and I have found, indeed, that there is a change, as Congressman Ratchford just indicated earlier, that there has been a change, I think, in the spirit about which the VA is going about to do its business. I don't take any credit for that. I think that the issue of agent orange is one that, quite obviously, demands a sensitivity and a compassion and a dignity for anyone who thinks that they were exposed. I continue to think that way. I think the VA is responding I think there are—with 235,000 people in any agency—that there are people who are nonbelievers, no doubt. But I would think that the majority of VA employees are very concerned about this issue, and I think that I can speak for them.

Mr. **McEwen**. Are you absolutely satisfied and can you assure this committee that the Veterans' Administration is doing everything possible to obtain the facts with respect to any disabilities which may be due to agent orange?

Mr. **Walters**. I have spent hours with Dr. Custis on that very subject and I am convinced that our medical department is doing everything it can do to get the final solution and the answer to this problem.

But, as I just submitted in my statement, I believe the final solution to this, hopefully, will lie with the Centers for Disease Control Epidemiological Study which was mandated by the Congress—and hopefully it will give us the final solutions to these problems.

In the meantime, the VA continues to work on birth defect studies, a twin study and other studies that are ongoing as well, and I think they are working at it with no preconception of the results, but to find the medical facts which will make us able to make a final conclusion as to what disease may or may not have been caused or have a service connection—not a cause, but a time-related incidence back to service which will allow us then to compensate, if indeed compensation is needed.

Mr. McEWEN. Mr. Administrator, those of us like myself that are concerned about this issue sense the extreme frustration that Congressman Ratchford articulated earlier. As a result, we are searching for any opportunity to vent that frustration because there seems to be an inability to resolve it. Veterans' Administrators have often been a source where Congressmen can vent their frustrations. I wish to assure you that we look forward to working with you to resolving it so that all of us can do what is right by America's veterans.

Thank you very much.

Mr. APPLEGATE. Thank you, Mr. McEwen.

Mr. Montgomery.

Mr. MONTGOMERY. Thank you, Mr. Chairman. I would like to welcome the Administrator and Miss Starbuck and also Dr. Custis and Mr. Murphy back before this subcommittee and back before the Veterans' Affairs Committee.

I think everyone in this room today, Mr. Chairman, would really like to get to the bottom of this issue on agent orange and if it is a major problem with the Vietnam era veterans, we certainly ought to do something about it and we ought to take care of it and we ought to compensate or see that those veterans are taken care of.

A couple of problems—Mr. Daschle knows how I feel. I am concerned that we will spend about $100 million to get to the bottom of this agent orange and it takes time and I think we ought to move not slowly, but we should move in a manner that will produce a thorough and factual study. In the report from Australia pertaining to agent orange, they pointed out when we were over there meeting with veterans officials that the Vietnam era veteran really had other problems, more serious, they thought, than agent orange, and if they have got these problems we ought to definitely concentrate on that and be sure that we are moving in the right direction on agent orange.

Of course, I am open to considering the bill that Mr. Daschle and others have signed and introduced. Having said that, I only have one question, and maybe this should be directed to Dr. Custis, pertaining to chloracne and also to liver diseases that could be caused by dioxin. I noticed this bill of Mr. Daschle's doesn't have a time limit of exposure.

When does this chloracne and liver diseases show up—when do liver problems show up after being exposed? How long afterward? Is there any time limit on it?

Dr. CUSTIS. In the case of liver damage, and specifically porphyrias, it may appear anywhere from 6 weeks to 6 months, the symptoms and the signs. In the case of chloracne, a matter of a couple of weeks. In both cases, the evidence at hand would indicate that both of those are acute manifestations that are self-limited in time. There's no latency in their occurrence; that is, the onset occurring beyond those 6 weeks to 6 months that I referenced.

Mr. MONTGOMERY. In other words, having an open-ended bill in that area would not be quite logical. Is that what you are saying?

Dr. CUSTIS. Yes, sir. There is no doubt that dioxin is an extremely toxic agent causing severe, acute disability. The problem that we face and the answer that we are trying to seek is, in dioxin exposure, the cause of such delayed disabilities, and more importantly, what is the time frame between exposure to a noxious agent and the onset of these disabilities.

Mr. MONTGOMERY. Thank you, Mr. Chairman.

Mr. APPLEGATE. Thank you, Mr. Chairman. The gentleman from Arkansas, Mr. Hammerschmidt.

Mr. HAMMERSCHMIDT. Thank you, Mr. Chairman. I, too, want to extend a warm welcome to Mr. Walters, Dr. Custis, Miss Starbuck, and Mr. Murphy as our first witnesses this morning from the executive branch.

Do you know of any studies that are accepted as being valid by the medical community that conclude that soft tissue sarcomas are related to exposure to agent orange, and I direct that to you, Dr. Custis.

Dr. CUSTIS. Yes, sir. The studies that precipitated this concern were the Swedish studies, two in number, performed by the same investigators, the investigators themselves saying that they were "suggestive of" an increased incidence of soft tissue sarcoma. Since then there have been multiple studies either gotten underway or finished that have not, in all cases, verified the suggested findings of the Swedish studies.

I would defer to Dr. Shepherd who is here with us who can address that in very specific detail if you are interested in a number of those studies.

Mr. HAMMERSCHMIDT. Is Dr. Shepherd on our witness list or is he just accompanying you?

Dr. CUSTIS. He is just accompanying us.

Mr. HAMMERSCHMIDT. If you would supply that information for the record, I think it would be a more complete record.

[Subsequently, the Veterans' Administration furnished the following information:]

Soft-tissue sarcomas are a diverse group of uncommon cancers. Authorities disagree as to exactly which tumors belong in the group and those included do not have a common cause, comparable progression, or treatment.

An association of soft-tissue sarcomas with exposure to phenoxy herbicides, such as those in Agent Orange, was suggested by two Swedish studies of foresters and farmers. Both were conducted by the same group of investigators who estimated about a five-fold increase of cases among the workers.

Seven cases of such sarcomas were found in four separate reviews of American chemical workers. The reports do not include the number of workers exposed to the chemicals, making it impossible to calculate whether the exposure increased the risk developing soft-tissue sarcomas.

Other investigations in Finland and New Zealand do not support the suspected increased risk of soft-tissue sarcomas from exposure to the ingredients of Agent

Orange. Neither does the experience among American farmers and foresters. The conflicting results, preclude a consensus that Agent Orange or its ingredients are causal agents in the development of the soft-tissue sarcomas.

Mr. HAMMERSCHMIDT. I suppose, to sort of summarize what you are saying in layman's terms, in the medical community or in the scientific community, the jury is still out on this subject. Is that correct?

Dr. CUSTIS. That's right, Mr. Hammerschmidt.

Mr. HAMMERSCHMIDT. What specific training has been given to doctors who give agent orange examinations around the country, Dr. Custis?

Dr. CUSTIS. There have been two conferences with an extensive agenda of an educational nature and since that time, regular telephone conferences keeping those individuals, the environmental physicians, up to date on new happenings.

If I may just take advantage of that question to offer the observation that there are 190,000 people in our system that come in contact with our veteran patients, including some 11,000 physicians. I think there is no doubt about it back in 1979 and 1980 when everyone, including the VA, were becoming more and more aware of the significance of agent orange, that there were, indeed elements within this system that had a high level of doubt.

I submit that any reference to insensitive physicians today is essentially anecdotal and must be by exception. I am absolutely convinced that the great majority of those who are charged with giving agent orange physical exams and, in general, caring for these veterans are extremely sensitive and very empathetic as to the justifiable concerns of our veterans.

Mr. HAMMERSCHMIDT. Assuming that a veteran was exposed to agent orange in Vietnam and assuming that he or she was diagnosed today as having chloracne, what would you predict with respect to VA's action on a claim for service connection for the disability?

I address that to whoever you feel could best answer.

Mr. WALTERS. I think Dorothy Starbuck could answer the question more precisely perhaps.

Miss STARBUCK. Mr. Hammerschmidt, the evidence we have on which we base our decisions is that exposure to dioxin is a causative factor of chloracne, of skin disorders, and in the adjudication of claims from veterans who have claimed a skin disorder, some of them specifically claiming chloracne, we have allowed about 1,317 of those cases where exposure to agent orange has specifically been claimed. In other cases, we have allowed a great number of skin disorder compensable disabilities.

Mr. HAMMERSCHMIDT. Thank you very much.

Thank you, Mr. Chairman.

Mr. APPLEGATE. Thank you.

Yes, Mr. McEwen?

Mr. MCEWEN. Thank you, Mr. Chairman.

Miss Starbuck, has there been a case where a veteran has been diagnosed as having chloracne where a disability has been denied?

Miss STARBUCK. Not where a disability has been denied, no, sir.

Mr. MCEWEN. Thank you very much.

Thank you, Mr. Chairman.

Mr. APPLEGATE. The gentleman from South Dakota, Mr. Daschle.

Mr. DASCHLE. The only thing I would add to the question just posed by Mr. McEwen is that the doctors I have talked to in VA hospitals say that it's very difficult to distinguish a serious case of acne and chloracne and there are many cases where veterans have developed a very serious case of acne and have not been compensated because they were told it wasn't chloracne. So there is a difference if they say it is chloracne officially, then I think that compensation is warranted, otherwise it isn't.

Dorothy, I want to tell you that I was out in your stomping grounds a month or so ago and I really want to commend you for laying the groundwork for what I think to be one of the finest regional centers in the country. I am very impressed with the people out there. I am very impressed with the hospital, under the very limited conditions with which they are working, and I am pleased with what I saw in my recent trip to Denver.

They work under very difficult conditions with limited assistance technologically and a large part of what they attribute to their success is attributed to the leadership that you provided when you were there, and so I wanted to commend you for that.

I share the view of a lot of people who have expressed the same view that the doctors and many others in the hospitals across our country are really doing a lot. I talked at length with the doctor giving the agent orange physicals in Denver and they do have the sensitivity that Don addressed, and so it's not there that I lay the fault or the blame and it certainly isn't with Mr. Walters alone because, as he said, we have had prior Administrators who share his view.

But I really challenge a statement by any Administrator who says, "Yes, indeed, we are doing all that we can do." That simply is not true and I guess we just have a difference of opinion here. If we know that dioxin seriously kills animals when we test it on animals, if we know that, it seems to me that we owe them the benefit of the doubt until we get all of the information and that we ought to be able to give them the treatment that they require and the compensation that they deserve, but we aren't doing that today.

Now if we were doing that, I would share the view that you have expressed that, indeed, we are doing all that we can do, but we are not. So it begs the question, why in heaven's name do we not give them the benefit of the doubt? And in answer to the chairman's question about, "Well, maybe we need to wait." Well, maybe we do need to wait before we get all of the information, but again, we have a sunset in my bill, we have a provision right in the law that say, "Look, if there comes a day when we cannot prove far more substantially than what we can today—in fact, we have even set a deadline, after the CDC study is in, that if information conclusively shows that there ought not be any compensation the program will be eliminated. But then for us to say in the meantime, "Veterans are going to have to wait," certainly does give you the opportunity, it seems to me, in a bona fide way, to say, "We are doing all that we can".

Now we talk about the Australians and I think it has been clear that the records are that the Australians weren't exposed to agent orange like our people were. The Centers for Disease Control testified that, "If we are looking for some kind of a causal relationship, forget it." This study, I don't care if it costs $300 million, is not going to give us a causal relationship. So we might as well just keep waiting for 30 or 40 more years because that kind of a causal relationship probably will not exist.

Now we talk about facts and you said, "The facts just don't show that there is any justification, even for now, to give the presumptive doubt to these veterans until the so-called 'facts' are in." We didn't have the facts for cardiovascular disease for amputees. You know that, and I have talked to a lot of people privately in the VA and they say, "You have got us on that one."

Well, I know I have got you on that one, but that doesn't change your situation here. I would like to see where the facts show that there is a causal relationship. We can say the same thing for multiple sclerosis, where is the causal relationship there?

I guess the bottom line is—I really take exception to the statement that we are doing all that we can. We're not asking for everything that I possibly could hope to have in a compensation program for these veterans. We are not asking for that today. With three diseases we are saying, "Let's at least give them the benefit of the doubt. Let's respond to the veterans who just, for God's sake, have waited so long."

I know I am out of time, but the last thing I would say—and I had even hoped to ask some questions—is looking through the record, I don't recall a time when the VA officially came before the Veterans' Committee and said, "Yes, we support this change on presumptive disability." There are 40 of those disabilities on the books today—there may have been some, but I, in a cursory look, could not find one where the VA, prior to the time it was enacted into law, supported a presumptive disability to be added to the list.

I am out of time, Mr. Chairman, but I thank you for this and I do appreciate your coming back. I know you are busy man and I am glad we had the opportunity to hear you.

Mr. APPLEGATE. Mr. Daschle, insofar as you are the sponsor of the bill you may take an additional 5 minutes if you so desire.

Mr. DASCHLE. I won't even need to take 5 minutes. I have just a couple of questions.

In private I have talked to the PVA, I have talked to the DAV and they have told me—and I am not going to lay the blame on anybody, I am not passing on rumors—but I have been told, unequivocably, by more than one official in both organizations, "We were told if we support this legislation"—and I am not even going to say who told them, although they have made reference to those who have passed this on by more than one source—"that we will obliterate the presumptive disability of the compensation program in the VA today, if we support this legislation. So we have no choice. We can take their word or your word." I say, "You are not going to do that. We are not going to jeopardize the program."

Tell me this: If we have already set out 40 presumptive disabilities, if we have a cardiovascular compensation program for amputees based on, as I understand it, one study, how is it that this particular bill is going to so jeopardize the compensation program when we have already established the precedent in other areas?

Mr. **Walters.** I was waiting for the question, with baited breath. I am going to answer the question, but I don't know which one to address first. I will take your last one first. We do not agree with you on cardiovascular disease. "You do not have us", quote, unquote, because the medical community will not support your statement—not that I won't support it or deny it, but the medical community won't.

The National Academy of Sciences did a complete research of all the papers and went through a peer review and the whole thing on that study. I just went through it yesterday afternoon. So we don't agree—the medical community doesn't agree with you.

And then one other thing that I would like to point out to you is I caution you not to put words in Jack Powell's mouth, because I want to tell you, I have known that man and he will stand on his own judgment when he wants to and he, in private or in public, will disagree with your statements about somebody telling him what would happen to his compensation program if your legislation passed. He has his own thoughts and he expresses them quite well. I try never to put words in his mouth.

Mr. **Daschle.** Well, don't get me wrong. I want to direct——

Mr. **Walters.** I just wanted to clear the record, Mr. Congressman, to make sure we got that straight.

Mr. **Daschle.** Let's clear the record and I would hope that we could do so in a civil tone. My feeling is that I am not getting reports from within the DAV, within the PVA, within other veterans organizations, and I am not going to attribute it to any one director or any one individual, but there is no question but that people within both organizations have been told that and they will say it to me and they will say it to others, and I just want private statements to be made public.

I think it's important when we look at what reasons are given for their opposition that we relate that. I am not going to relate it to any one individual. But it is a fact. That is what I have been informed, and I think it's important for the public record to show that.

Mr. **Walters.** Well, if you wish to have them inform your committee, bring them in front of your committee and let them inform you. I do not know of that and I would be the last one in the world to accuse the PVA or the DAV or members therein of not subscribing to the views to their organization, in public or in private.

The other thing I wanted to mention—when you said, "Doing all we can," Mr. Congressman, we never do all we can, of course. There is no one in the world that does everything he can. If we did everything we could do, there wouldn't be any problems in this world of ours. But there are problems and there are challenges and the challenge is clearly in front of the Veterans' Administration. Under my leadership we intend to tackle those challenges with a positive attitude to get done what is best for the veteran.

We are going to do it with facts, we are going to do it expeditiously, we are going to do it the best way we know how. We will fail on occasion, but we will not lose sight of the fact that our constituency must be served, all of our constituency; and, in this particular piece of legislation, all of the constituency in the veteran community is not in support nor is this agency. I wanted to make clear to you in my opening statement that that's the way I feel about this legislation because I think I have got to represent our constituency here in front of this subcommittee and in front of the general public. When the constituency is split as widely as it is on the agent orange issue, it makes it difficult.

I don't sleep well at night. I am sure you don't either.

Mr. **Daschle**. Well, I commend you for your goals and for trying to articulate those goals and carry them out. I guess I take exception with the way in which you are trying to carry out the goal of trying to assist those veterans who may have been exposed to agent orange. It's clear, in my opinion, and I think in the opinion of the vast majority of Vietnam veterans, that the Veterans' Administration has not responded to those needs, to that constituency. I don't think you have a division of viewpoint within the Vietnam veterans and their constituency on this issue.

I think the overwhelming sentiment is that we need to address the agent orange issue far beyond what we have done thus far.

Mr. **Walters**. I agree.

Mr. **Daschle**. If we make the statement that we are doing everything that can be done, we have to be careful with what we are saying when we say, "everything we can do."

Mr. **Walters**. I agree.

I also agree that we must do more. We must always do more. When you and I disagree, your legislation and the agency's position disagree, is in the methodology in which you are going at it. We disagree with that. We are representing the DAV and the PVA and their compensation, we are representing the agency views on it and we disagree.

Mr. **Daschle**. Well, I guess I am out of time again. If I could just, in summary, say, if we know it kills animals, if we know that it is as toxic as it is, why in heaven's name can't we give the benefit of the doubt to the veterans for a few years?

Mr. **Applegate**. Thank you, Mr. Daschle.

The gentleman from Texas——

Mr. **Murphy**. Excuse me, Mr. Chairman. If I could interrupt, Mr. Daschle brought up a point and I would like to make a few comments directed to him by way of clarification.

Mr. **Applegate**. Yes, go ahead.

Mr. **Murphy**. In hearings in the House and in the Senate the term "causal relationship" keeps being bandied about and I would just like to state the legal position under Veterans' Administration law in title 38, hopefully, to clarify a little bit what the legal requirements really are.

Of course, the guiding term or consideration is service connected. To be service connected, a disability or injury must be incurred in or aggravated during the period of military service. When we say "connection," we mean connection in point of time to the period of service. We are not talking about a necessity that we know in a medical, scientific sense, the exact causative agent that may trigger a disability whether it be a disease or an injury. The connection is to the period of service.

Thank you very much, Mr. Chairman.

Mr. **Applegate**. Thank you very much.

The gentleman from Arkansas, Mr. Hammerschmidt.

Mr. **Hammerschmidt**. Mr. Chairman, I think it might be appropriate to our hearing record, and I ask unanimous consent that we put the references in on the studies that were made on cardiovascular conditions that occur in double amputees and severe single amputees. I know that two studies were made, one by the National Academy of Sciences and one by the DAV. We need not put the studies in but put the references to those studies so that we would have a complete understanding of what the facts are on this.

I would ask that the staff prepare the references and put them in the record at the appropriate point.

Mr. **Applegate**. Without objection, that will be done.[1]

Are there any other questions or comments that anyone would like to make at this time?

In that case, thank you very much. I don't think that there are any questions in the minds of any of us, nor you, that we all seek to achieve the same goals and we all have the interests of the veterans at heart. We know that you do and I am sure that you know that we do. Although we may not always travel the same roads toward those goals and while we may disagree at times, we hope that reasonable people will be able to sit down and work together until we achieve those goals.

As the chairman of the subcommittee and speaking on behalf of my colleagues, we once again appreciate your coming in today. The cooperation of the Veterans' Administration and of your associates is always something to which we look forward.

Thank you very much.

Mr. **Walters**. Thank you, Mr. Chairman.

Mr. **Applegate**. This morning we have with us Maj. Gen. Murphy Chesney, who is the Deputy Surgeon General, Department of the Air Force who is going to present to the committee the Ranch Hand study, the primary purpose for which the meeting is taking place this morning.

We welcome you, General Chesney, to the committee and we look forward to hearing what you have to submit to us.

Your prepared statement, will be entered into the record. However you may wish to present your testimony, we will leave that within your hands.

You may proceed at any time.

---

[1] See House Veterans' Affairs Committee Print No. 7, 96th Congress.

STATEMENT OF MAJ. GEN. MURPHY A. CHESNEY, DEPUTY SURGEON GENERAL, DEPARTMENT OF THE AIR FORCE, ACCOMPAINED BY COL. GEORGE D. LATHROP, CHIEF OF THE EPIDEMIOLOGY DIVISION; COL. PATRICIA M. MOYNAHAN, CHIEF OF THE OCCUPATIONAL EPIDEMIOLOGY SECTION; AND DR. JOEL E. MICHALEK, MATHEMATICAL STATISTICIAN, DATA SCIENCES DIVISION; ALL FROM THE USAF SCHOOL OF AEROSPACE MEDICINE, BROOKS AIR FORCE BASE, TEX.; AND ACCOMPANIED BY JACK R. SPEY, PRESIDENT, RANCH HAND VIETNAM ASSOCIATION, MAJOR, USAF (RETIRED)

General CHESNEY. Thank you, Mr. Chairman. I would like to give a brief summary of my statement and then be prepared to answer questions.

I am accompanied by Col. George D. Lathrop, Chief of the Epidemiology Division; Col. Patricia M. Moynahan, Chief of the Occupational Epidemiology Section, and Dr. Joel E. Michalek, Mathematical Statistician, Data Sciences Division; all from the USAF School of Aerospace Medicine, Brooks Air Force Base, Tex. I am also accompanied by Jack R. Spey, the president of the Ranch Hand Vietnam Association. Mr. Spey is a Vietnam veteran who served five separate tours in Vietnam and has 7 years of experience flying in herbicide aircraft.

We appreciate the opportunity to present an update on the progress of the Air Force epidemiological study of Ranch Hand personnel exposed to herbicides in Vietnam between 1962 and 1971.

The Air Force has now completed the first mortality study and I will present the results of this baseline mortality study to you today.

The 1,269 individuals who were assigned to Air Force units directly involved in Operation Ranch Hand were identified through an extensive search of military historical and personnel records. These men were generally exposed to the herbicide for up to 10 or 12 hours a day, 5 to 6 days a week for periods of at least 1 year. Thus, the Air Force considers them to be the most heavily herbicide exposed group of U.S. military personnel in Vietnam.

For the purpose of statistical comparison, a group of other Air Force personnel assigned to duty in Southeast Asia was selected. They were matched to the Ranch Hand group by race, job, and date of birth. Five comparison subjects were selected for each of the Ranch Handers to improve the ability of the study to detect a difference in the death experience.

The death experience of the herbicide/dioxin-exposed group was contrasted with the death experience of the matched group and three other groups external to the study—the 1978 U.S. white male population, a Department of Defense retired population, and the 1956 class of West Point.

All Ranch Hand and comparison subjects designated as killed in action were removed from the study population. Analysis of these killed in action deaths will be performed for the next annual report of the mortality study. As of December 31, 1982, 50 Ranch Handers and 250 comparison subjects had died—certified on or before April 25, 1983. This represents only 4 percent of each group. No statistically significant differences in the crude death rates were found between the Ranch Handers and the comparison group. There were no soft tissue sarcoma deaths diagnosed in either group.

Analysis showed that, to date, the mortality of the Ranch Hand group is identical to that of the matched comparison group. The overall rates and causes of death are not statistically different between the groups. However, it does appear that the officers are living longer than the enlisted personnel in both groups. The Ranch Handers did show a relative decrease in cancer but an increase in liver disorder deaths. However, both of these findings are not statistically significant at this time.

The number of cancers is small, but the morbidity data that we hope to release in October will include cured cancer cases, ongoing cancer cases, and recorded cancer deaths.

The digestive system mortality is submitted for the record.[1] While these findings are preliminary and statistically nonsignificant at this time, they represent a key area of interest for continuing analysis.

Analysis of both the overall Ranch Hand and the overall comparison groups to the 1978 U.S. white male mortality experience showed highly significant findings of less mortality than for the equivalently aged U.S. white males.

The DOD retired and the West Point data were used for further analyses in an attempt to better define the healthy worker effect. The contrast with the DOD data again demonstrated significantly less mortality for the Ranch Hand officers, comparison officers, and comparison enlisted men. The Ranch Hand enlisted group did have a favorable mortality experience but not to a statistically significant degree.

In summary, the mortality analyses described in this report have not revealed any adverse death experience in the herbicide/dioxin exposed group. The results of the analyses, regardless of the source of the comparison data, were consistent.

At this time there is no indication that the Ranch Hand personnel have experienced any increased mortality or any unusual patterns of death in time or by cause. They are not dying in increased numbers, at an earlier age, or by unexpected causes. However, the fact that the adverse effects have not yet been detected does not imply that an adverse effect may not become manifest at some time in the future. For this reason, further analyses are intended and the mortality in the study population will be ascertained annually for the next 20 years.

The analysis of the data collected during the questionnaire and physical examination phase of the Ranch Hand study is well underway and proceeding on schedule. The report of this aspect of the study will be reviewed by the Advisory Committee on Special Studies Related to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants. We anticipate that the report will be made available to the public in October.

We will be happy to try to answer any questions at this time, Mr. Chairman.

Mr. APPLEGATE. Thank you very much, General.

---

[1] See "Project Ranch Hand II," on p. 82.

I appreciate your testimony very much. It will be very helpful to us in present and future deliberations. I am sure there is going to be a considerable number of questions that will be asked because of this study and what it is going to mean in the long run.

You stated that there was a higher incidence of mortality amongst the Ranch Hand enlistees; is that correct?

General **Chesney**. Yes, sir; that is true.

Mr. **Applegate**. And I assume that those that you are talking about would be primarily the foot soldiers, the ones that were down on the ground.

General **Chesney**. Those who worked in the back of the aircraft, in flying it, who loaded the aircraft, and those who worked in operations on the ground.

Mr. **Applegate**. But you said, even at that, there wasn't a significantly higher incidence of mortality.

General **Chesney**. It's not statistically significant when looked at by a statistician at this time.

Mr. **Applegate**. How much higher? And let me ask you this: Why did they die? How did they die?

Colonel **Lathrop**. Ranch Hand enlisted deaths included four from cancer.

Mr. **Applegate**. What kind of cancer?

Colonel **Lathrop**. I believe it was a broad spectrum——

Mr. **Applegate**. Your microphone doesn't seem to be on. Could you get up closer to the other microphone?

Colonel **Lathrop**. We have those mortality figures if you wish to see them on the draft. They are submitted within the body of the report. There are four cancer deaths within Ranch Hand enlisted personnel. That actually represents a paucity of cancer with respect to what we would anticipate in the Ranch Hand group.

Mr. **Applegate**. General, I wonder if you would identify for the committee, who the people are who are accompanying you today.

General **Chesney**. I am sorry. This is Col. George D. Lathrop, Chief of the Epidemiological Division of the School of Aerospace Medicine. This is Col. Patricia M. Moynahan, the Chief of the Occupational Epidemiology Section of the School of Aerospace Medicine. This is Dr. Joel E. Michalek, the mathematical statistician from that school, and this is Mr. Jack E. Spey, the president of the Ranch Hand Vietnam Association.

They are here to answer any questions you have about the Ranch Handers; what they did, how they flew, how they lived, and that sort of thing.

Mr. **Applegate**. Well, thank you very much, and we certainly do welcome all of you to the committee and appreciate that you have made yourselves available for questions.

At this time, I would recognize the gentleman, my colleague from Ohio, Mr. McEwen.

Mr. **McEwen**. Mr. Chairman, if I could at this point yield my time to the representative Congressman from Oregon who was actively involved in Vietnam in this area. I will allow him to submit his questions on my time.

Mr. **Applegate**. Mr. Denny Smith?

Mr. **Denny Smith**. Thank you, Mr. Chairman. I think I may be the only one on the subcommittee that served a tour in Vietnam. I was a bluesuiter and flew F-4's out of Cameron Bay in 1965 and 1966. We dealt with areas where the Ranch Hands were operating from time to time and I know that to plod along down there in those airplanes with the amount of lead that was coming up had to be a real fun experience, let alone handling chemicals similar to what the airborne bugkillers throughout this country have used in the agricultural community for a long period of time.

As I look at this study and as I look at the friends that I have in the aviation business involved in the delivery of chemicals onto crops for the food that we are able to enjoy, I was never very impressed with the success the Ranch Hands were able to have in a 100-foot canopy of jungle. There is an awful lot to kill before you can really get down and see what is underneath.

Unfortunately, I am sure that the people who flew the airplanes in Vietnam were much more concerned about the lead poisoning they might receive from those shooting at them from down on the ground than anything else that they might have been handling, especially in light of the fact that so many people have delivered this chemical for so many years in our own agricultural community.

One of the things that has bothered me all along about this issue has been the relative absence of hard facts pointing to service-related disability. Certainly if we have people who have handled something and have some kind of disability, no matter what it is, that comes out to a service-connected situation. We would like to see them taken care of and I think everybody on the committee would certainly agree with that.

And this study was authorized, as I understand it, to try and really decide whether anyone exposed to agent orange had been injured and to statistically try and lay out what the problem really is here among the Vietnam veterans who served in the Vietnam area and who were exposed to the chemical.

In this study you are pretty certain obviously, that the Ranch Handers are the group most affected and most exposed to agent orange. I think the committee was very pleased with that analysis. Obviously, this report has got a lot of pages in it, but are you certain that you have pretty well identified everything? You might just expand on that a little bit, if you would, General.

General CHESNEY. That this is the most affected group?

Mr. DENNY SMITH. Yes.

General CHESNEY. I think that we are in agreement on that. We have done some studies that show that the people on the ground were maybe 1,000 times less exposed than the personnel in the aircraft. We sprayed on triple canopy, primarily in enemy-held territory. There have been studies to show that less than 10 percent of the agent that sprayed got to the ground through this canopy. The people on the aircraft daily flew in it, flew in contrail, got the stuff in the aircraft, got it on their hands when they were pumping it in. I will let Mr. Spey address any more of that.

Mr. SPEY. Mr. Chairman, Congressman Denny Smith, you have alluded to the methodology of the application similar to dusting organizations back in Oregon or out West or anywhere else. Our method of loading, flying, and application was very similar to that. I think we have all seen file films on it.

Mr. DENNY SMITH. Did you single-point load the chemical?

Mr. Spey. Sir?

Mr. Denny Smith. Did you single-point load the chemical?

Mr. Spey. Yes, sir, it was just a nozzle through a hole.

Mr. Denny Smith. It was a nozzle connection and then a pump that would pump it into the tanks in the airplane there.

Mr. Spey. That's right, sir, and you had spillage in the cargo compartment that was present when you preflighted the airplane.

Mr. Denny Smith. I used to do that when I was a kid. I loaded both spray and dust and it's a messy job, no doubt about it.

Mr. Spey. It was messy for our people so I think the choice of the Ranch Hand operation as the group that was studied for scientific purposes is respected.

Mr. Denny Smith. Well, I don't doubt that it was a very hazardous occupation, having watched it in operation.

In going into the major jungle areas where we did have 100-foot of canopy in the enemy-held territory and where we were trying to get at the trails—I mean, this was not just indiscriminate laying of the chemical; it was an attempt in certain areas to realistically try and penetrate all the way through and destroy all of the foliage, correct?

Mr. Spey. In the case of the use of defoliation as a strategic weapon type of application, you didn't kill trees in 1 month. It was anywhere from 3 to 6 months. The foliage died and you had a significant increase in vertical visibility. In other words, the ground troops didn't come in and say, "Come in and spray on top of me to kill all of these bushes so I can see what I am doing". It simply was not capable of producing those kinds of results.

Mr. Denny Smith. I have had people try and call in napalm right on top of them though to try and keep the——

Mr. Spey. It's much more effective with napalm.

Mr. Denny Smith. Yes.

What areas did you basically lay down trying to get at the canopy? Basically out to the Laos border through Pleiku from the coast? That was one area, wasn't it?

Mr. Spey. Yes.

Mr. Denny Smith. Why don't you just kind of delineate the specific areas that you operated in in the heavy jungle?

Mr. Spey. During the time frame I spent there, war zone D, for example, Boi Loi Woods—there we tried to defoliate, dry up the foliage and subsequently set it on fire and it didn't work very well.

Mr. Denny Smith. But you didn't defoliate the whole country though?

Mr. Spey. Not me personally, sir.

Mr. Denny Smith. No, but I mean basically they were working on highway areas. It was very specific.

Mr. Spey. Some of the work was lines of communications, to try to kill the foliage to suppress the possibility of ambush. Some of the work was large areas of foliation to try to open up vertical visibility. Of course, probably the most productive work was in the area of crop destruction, which just put an additional logistic burden on the people by killing their crops.

Mr. Denny Smith. Thank you very much.

Mr. Applegate. The chairman of the committee, Mr. Montgomery.

Mr. **Montgomery**. Thank you, Mr. Chairman.

General Chesney, let me congratulate you and your task force for taking on a tough job and then after you did the job, you gave the results to the American public. I saw you on one of the TV news shows and I thought you handled yourself very well. You told it like it was.

I have been involved when you have to tell people some tough things they don't like to hear. But in government, you have to take strong positions and unpopular positions at certain times and I want to commend you. When I saw you on television you showed yourself as feeling very strong about the report.

And right after you were on this news show a veterans group who feel very strongly about agent orange made the statement, "Well, we can understand that because those Ranch Hands could come home every night after a mission and they could take a shower. Those fellows on the ground are the ones that we are talking about."

Does this have any validity, any strength to it or did you have the opportunity to look into that area also?

General **Chesney**. Yes, sir, Mr. Montgomery, we have. I would like to ask Mr. Spey to answer that part of the question.

Mr. **Spey**. Congressman Montgomery, we loaded, handled and delivered the herbicides without using any kind of protective clothing as there was none required. I think science will support that none is required right now. Our people worked with the chemicals from an everyday operational standpoint. We practiced normal individual hygiene. At the end of a flight day you might leave the flight line and go to your quarters, say, at 1 o'clock in the afternoon or sometime around that time.

If you felt hot and sweaty at that time, which you often did in Vietnam usually starting about 8 o'clock in the morning, you might then take an ordinary bath or a shower. But there were no unusual hygienic practices undertaken.

As far as physical contact was concerned, it occurred during the preflight of the airplane. You were smelling and aware of the fumes when the airplane was being flown. The ground maintenance personnel were removing and replacing mechanical parts with the chemicals present both inside the airplane as a result of spillage and also on the ramp—you know, on the ramp area surrounding the airplane—so that it was an everyday industrial-type of contact with these different chemicals, certainly not casual contact.

Mr. **Montgomery**. Thank you, sir.

General Chesney, I guess what I am trying to get into is the difference between the Ranch Handers and the GI soldier out with an infantry unit. As you said, only 10 percent of the American forces were exposed. Is there any difference in the exposure between that fellow on the ground, in a foxhole, and those who the gentleman just testified about who were handling it every day?

General **Chesney**. None that we can determine.

There's at least one study, I think that shows that dioxin will be absorbed into the skin pretty thoroughly within a 4-hour period, if you are exposed to it. Ranch Handers did drink coffee on the airplane. First thing after they levelled out on their flights was that the crew chief would bring everybody a cup of coffee. So it was in the coffee and they got it in their nose in their mucus membranes and they would swallow that. There was not one of them hardly that did not know the taste of the stuff.

So what we have looked at makes us believe that there was tremendously more exposure to those in the aircraft and the ground crew than was the average troop whom we did not try to spray, who was sprayed only casually if it happened.

Mr. **Montgomery**. I think, Mr. Chairman, that that's a really important point. We ought to get the record on that. I mean, if there was more exposure in the Ranch Hand group, then that certainly should be clear in the record. The subcommittee members should understand this. To shoot the report down by saying that those GIs on the ground had more exposure when they didn't would certainly, I think, not be exactly fair.

My time is up. I have only one more question. It seems to me that the Ranch Hand personnel have had less cancer than those that you had in the central groups. Is that correct?

General **Chesney**. Yes, sir, that's true.

Mr. **Montgomery**. Does that tie in with medical treatment—if you gave these chemicals to those who have cancer, you know, in our different hospitals and clinics? Does that have any logic to it that chemical exposure such as they had would reduce cancer?

General **Chesney**. That chemical exposure would reduce cancer? I don't know of any drug that will reduce cancer. Vitamin A, for instance, has been recently touted as doing that, but there is very little that shows us that anything would reduce cancer.

I think it's too early in our statistical report to draw any conclusions at all regarding cancer. When we have the morbidity study in October, we will have much better exposure data and can give you, I think, better answers about cancer. It may not go the same way as this has. I cannot answer that at this time.

Mr. **Montgomery**. Well, I am not trying to write medical history here—[laughter]—that was just of interest to me.

Thank you, Mr. Chairman.

Mr. **Applegate**. The gentleman from Ohio, Mr. McEwen.

Mr. **McEwen**. General, I just wanted to welcome you to this committee and tell you that we appreciate your testimony. I would ask of Mr. Spey one brief question. Let me tell you what I have been told in my personal investigation and then tell me whether or not it is the case.

I was told by veterans that it was traditional to dilute this agent orange up to 100 parts, 100 to 1, and that many times rather than that being done, it was used straight. Is that a possibility?

Mr. **Spey**. Sir, the chemical was delivered in 55-gallon drums. As you know, they were color-coded so that we could understand what was in them. I certainly couldn't say the scientific name for them; it was stenciled on the can. Those containers were pumped into a 1,000 gallon holding tank and pumped directly into the airplane. Later on they were pumped out of the 55-gallon drums into surplus fuel trucks so that the aircraft could be reserviced.

Mr. **McEwen**. So there was no dilution?

Mr. **Spey**. Only in my backyard, sir.

Mr. **McEwen**. Was there supposed to be some?

General CHESNEY. No, sir, it was 100 percent concentration of the two active agents that were sprayed. Now there were many things sprayed in Vietnam and what some of the troops on the ground may have thought was agent orange could have been malathion to kill mosquitoes. We sprayed the troops to kill mosquitoes, there is no question about that.

Mr. McEWEN. Thank you very much.

General CHESNEY. Yes, sir.

Mr. APPLEGATE. Thank you, Mr. McEwen.

Let me just ask a quick question. Are the Air Force and the Army still using the herbicides?

General CHESNEY. No, sir, it has not been used since 1970 and I think it has been taken off the commercial market in the United States also.

Mr. APPLEGATE. Why?

General CHESNEY. The Environmental Protection Agency in 1970 put out a ruling, I think, that it should not be used due to some studies that had been done in the late 1960s.

Mr. APPLEGATE. What was the reason, General?

General CHESNEY. An animal study that was done by K. Diane Courtney and others for the National Institutes of Health that showed that 2,4,5-T could cause deformities and still-births in mice when administered in relatively high doses. That was first presented in the fall of 1969.

Mr. APPLEGATE. Are there exemptions to that? Is it under civilian use?

General CHESNEY. One of the ingredients, the 2,4-D is now in civilian use and is the active ingredient of most of the herbicides that you buy today to put on your lawn. 2,4,5-T, to the best of my knowledge, is almost not being used anywhere in the world today.

Mr. APPLEGATE. That's because it has some very negative effects on the human body?

General CHESNEY. Because it had in it the contaminant dioxin. Dioxin was a contaminant in the 2,4,5-T and you almost cannot make it without dioxin in it so they have just about quit making it, primarily.

Mr. MONTGOMERY. Would the gentleman yield?

Mr. APPLEGATE. Yes.

Mr. MONTGOMERY. I have been totally involved in some cases having to do with dioxin. In the South we have had the fire ants and it's really a serious problem and it's on the way up here. Eventually it will get here; it's traveling north. One chemical, with a small amount of dioxin, was used for many years and it did keep the insect down. I don't think it was so much a case of hurting human beings as it was the alleged possible harm of the environment and also the animal life and plant life. But the fire ant will kill humans and also will kill newborn animals so it is a problem of which way you handle it. But the EPA just struck down the use of a new chemical that was developed in our State called "Ferriamicide"—I am getting off the subject—but we have no way to fight these insects and they have become a major problem in our State.

We had no deaths reported from the use of certain chemicals back several years ago but all that has been taken off the market now.

Mr. **Applegate**. I thank the chairman for that very useful information.

The gentleman from Texas, Mr. Hall.

Mr. **Hall**. Thank you, Mr. Chairman.

General Chesney, you indicate by your testimony that there has been no really firm statistical significance to the use or exposure of people to agent orange that may have caused their deaths.

General **Chesney**. Yes, sir, that's our statistical report so far.

Mr. **Hall**. Well, doesn't that run exactly counter to what Dow Chemical Co. has stated in those interoffice memos that have been exposed lately?

General **Chesney**. I am not privy to Dow's interoffice memos. I think the Dow people may have had more exposure, possibly, than the Ranch Handers. I would not want to try to compare those two groups.

Mr. **Hall**. Well, have you read any of the news accounts of the interoffice memoranda that have been released by a court order——

General **Chesney**. No, sir.

Mr. **Hall** [continuing]. In which the Dow Chemical people, as I understand it, said that there were serious questions about dioxin and agent orange, back in the 1960's, that was rampant in the company in Dow files?

General **Chesney**. I have been out of touch lately, have been on leave, had a daughter get married, and have not read any of those in the last few days, sir. I will look them up and read them though.

Mr. **Hall**. Well, have any of the other folks at the table read any of those articles about the Dow Chemical papers?

Mr. **Spey**. I have just seen a mention of it on television.

Mr. **Hall**. You mean none of you have read anything in the newspapers lately about the Dow Chemical Co. interoffice memoranda that have received nationwide exposure? That's strange.

Colonel **Lathrop**. I think all of us have seen that on TV.

Mr. **Hall**. Well, didn't those Dow Chemical Co. reports indicate that there might be some question about dioxin?

Colonel **Lathrop**. According to the TV reports, yes.

Mr. **Hall**. And regardless of why the environmental people took it off the market, they evidently had some question in their minds about the significance of excessive dioxin on animals, mice, and possibly human beings.

Now I am not saying that your Ranch Hand report is accurate or not accurate, but it appears to me that from what I have been able to read and what I have been able to hear from people who were in Vietnam, who were on the ground, who were dripping with this substance for sometimes hours or days at a time, it would lead me to believe that there is some significance to what these other outside sources have said about dioxin.

It's also hard for me to believe that a man in an airplane would receive as much exposure to dioxin as those on the ground who were actually handling it personally, becoming wet with the substance and who would not have had an opportunity to bathe and rid themselves of that. It is just difficult for me to believe that a man in an airplane who is dropping it, even though he might have had a cup of coffee or whatever you said—I just don't believe it's reasonable to assume that the man on the ground received less of it than the man in the air.

Colonel LATHROP. Mr. Hall, it's difficult for Air Force folks to reconcile your argument. We have done mathematical calculations to show that on the average folks on the ground received one-thousandths of the dose compared to an average Ranch Hander flying these missions. These folks were in direct liquid contact with the substance. When a hose broke on board that aircraft, they were literally doused in it.

We have demonstrated the interior tube action within the fuselage of these aircraft wherein the pilots and navigators up front would receive the vapors coming directly from the back of the aircraft forward out the cockpit window.

The anecdotal stories that we have heard from Mr. Spey and many of his comrades clearly indicate that their flightsuits were dripping with the stuff. They were in liquid contact as opposed to a person on the ground who may have received a mist-type contact.

Mr. SPEY. Sir, if I can add to that. We sprayed at the rate of 3 gallons per acre, the normal application to kill the foliage. That's equivalent to one one-millionth of a gallon per square foot. We assume that you and I have a vertical plane area of 1 square foot. This is excluding any foliage intervening. You and I would receive one one-millionth of a gallon as the airplane flew over you.

Mr. HALL. So suppose you receive that sort of a dosage daily for a week.

Mr. SPEY. Sir, we didn't spray the same area day after day for a week.

Mr. HALL. So you say that's an impossibility. I am not trying to argue the point.

Mr. SPEY. No, sir, but I think if you look at it realistically, we would spray one area and then come back, possibly 6 to 8 months later if it didn't look like we had obtained the desired results of foliage kill.

Mr. HALL. Well, as I understand it, it's the broad opinion of those who are here with General Chesney today that this chemical dioxin has not caused any appreciable damage to anyone who used it or who had it dropped on them from an airplane.

General CHESNEY. We have not said that, Mr. Hall. We have not said that in the least. We are giving an early preliminary death report only, and we are going to follow this for 20 years. What we tell you in October may be 180 degrees from what I am saying today.

Mr. HALL. What is going to happen between now and October.

General CHESNEY. We are going to complete the disease part of the study. We have looked at the dead. We have looked at the living. We are putting the data in a computer and come October, we are going to tell you how many of our Ranch Handers are sick compared to their comparison group and it may be a totally different story. We are very early with this.

Mr. HALL. Have any tests been made prior to this Ranch Hand Study?

General CHESNEY. There has been no statistical study in the United States of Vietnam veterans that I know of along this line, no, sir.

Mr. **Hall**. Have there been any studies of the Vietnamese people who may have been exposed to this dioxin?

General **Chesney**. Yes, sir, there have been some studies made and they have been done by Communist physicians and they are totally unreliable.

Mr. **Hall**. Thank you. My time is up.

Mr. **Applegate**. Thank you, Mr. Hall.

The gentleman from South Dakota, Mr. Daschle.

Mr. **Daschle**. Thank you, Mr. Chairman.

I am anxious to hear what the Congressional Medal of Honor's testimony will bring to light, especially as it addresses some of the questions posed very well here by Mr. Hall. I think that he may have an insight here that will be very valuable to us.

I would think also, and I am sure you would not disagree with this, that Army veterans dispersed this chemical in trucks and not in planes and, in some cases, disseminated that in a very different way. Isn't that right? So, if you say that, "None of the people on the ground received the exposure that those in the air received," I think you have to qualify that, do you not?

General **Chesney**. Yes, sir, we do. There was some spraying done from helicopters, there was some spraying done around bases.

Mr. **Daschle**. So it's important that we differentiate there because, obviously, those people had a much higher degree of exposure——

General **Chesney**. Yes, sir, that's true.

Mr. **Daschle** [continuing]. Than perhaps others on the ground.

I am most interested in page 58 of your testimony, the survival curve. It seems to me that when we look at enlisted personnel and when we look at that survival curve, I have a lot of difficulty not believing that that is statistically significant. Perhaps I should just have you describe that to me, if you will. It seems from a layman's point of view that when you look at that chart and you show those over 60 who are dying compared to those in the control group who had no exposure to agent orange, there's a dramatic difference between the two. I noticed in some of the news reports that that seemed to be one of the most significant facts here that we would want to bring out.

General **Chesney**. Yes, sir; that's very hard to explain and I would like to ask our statistician to do that, sir.

Mr. **Daschle**. OK.

Mr. **Michalek**. We have attempted to summarize the overall survival of the two groups by means of what we call confidence bands for their survival distributions. The comparison group is indicated by red and the black lines indicate the confidence envelope for the total Ranch Hand group, regardless of rank. So this summarizes——

Mr. **Daschle**. Excuse me, if you will. I know we are short on time and I want to make sure of something. Even though your report says that statistically there was a difference between enlisted personnel and officers—and I have got it on several different accounts here—when you look at the chart you blended both.

Do you have one that shows the difference between enlisted personnel who, according to the report, were more heavily exposed than officers, and can you show statistically on one of your charts the difference there?

Mr. MICHALEK. All right. Let's be more careful about what we are saying. We haven't said that the Ranch Hand enlisted have a higher death rate than the Ranch Hand officer, a significantly higher death rate.

Mr. DASCHLE. Well, let me quote here—do you disagree with Col. George Lathrop, the medical doctor?

Mr. MICHALEK. No, I am not disagreeing. What I am saying is that if you look at page 41, we have a summary of the findings of this report.

Mr. DASCHLE. Well, that doesn't really mean too much to me.

Mr. MICHALEK. Well, let me try to summarize it for you. The overall finding is that the Ranch Hand enlisted are equivalent to the control enlisted without regard to when they died or without regard to cause of death. OK?

The significant finding is that the control officers, where it says, "Internal Occupational Group Specific Findings," on the lefthand side about halfway down, there's a "CO" with a less than symbol and a "CE." That indicates that the control officers are living significantly longer than the controlled enlisted.

General CHESNEY. Well, let me try to put it to you another way. I think that 4.7 percent of the Ranch Hand enlisted are dead and only 3.8 percent of the Ranch Hand officers are dead. So the enlisted numbers—the mortality rate for enlisted personnel is higher than the mortality rate for officers. That's true and that has been true in almost every study that's been done on DOD personnel. Now whether this is an early effect of the herbicide and we will see this continue and get worse or whether it is a statistical anomaly, we are not sure at this time.

Mr. DASCHLE. Dr. Lathrop, in one of the reports in describing the study said, "We are concerned that because it conforms to the perception of these groups" that is, enlisted groups, "had far more exposure to the herbicides than officer personnel." So what he seemed to be saying here is that those who had a higher exposure level currently—now, that may be disputed, as you say, currently have a higher mortality rate?

General CHESNEY. Yes, sir, that is true.

Mr. DASCHLE. Well, that, to me, is a very significant fact at this point, and I am glad and very pleased to see that you qualify your answers by saying, "There may be more information in October or some other time."

General CHESNEY. There will be.

Mr. DASCHLE. But given the information we have today, you do not disagree with Dr. Lathrop's view that, "Those who had greater exposure, based on our statistics, have a greater mortality"?

General CHESNEY. Yes, sir. That's true.

Mr. DASCHLE. Thank you very much. This is very helpful.

Colonel LATHROP. Mr. Daschle, we felt obligated to point out that mild association, but also feel obligated to point out to you, as General Chesney has mentioned, that only 4 percent of the Ranch Handers have died to date and only 4 percent of the comparison group has died to date. It is difficult to make projections on that low mortality rate.

Mr. DASCHLE. Mr. Chairman, could I ask unanimous consent for just 1 additional minute?

Mr. APPLEGATE. You certainly may.

Mr. DASCHLE. Could you elaborate a little bit more on the significance of the liver disorders that you found? There seemed to be a very high significance, a significantly higher incidence of liver disorders, which, of course, is another issue we address in the legislation.

General CHESNEY. Yes, sir. We have looked at this carefully. We will look at it much closer between now and next year.

Mr. DASCHLE. In summary, would you mind just briefly——

General CHESNEY. There is a larger proportional liver death among the Ranch Handers than among the non-Ranch Handers, and a proportion of this is less of an alcoholic nature in the Ranch Handers than in the non-Ranch Handers. Now, this is death certificates only. Death certificates due to liver death are notoriously incorrect because physicians tend to be kind to their patients and not write down that they died of alcohol, primarily because it affects insurance and some other things. We are going to have to go and dig up everyone of those medical records, autopsy reports and look at that and give you a further report on that.

Mr. DASCHLE. How many enlisted deaths were liver-related?

Colonel MOYNAHAN. There are three enlisted deaths.

Mr. DASCHLE. That are liver-related. Very good.

Well, I, frankly, was a little concerned with the way in which this study was going to be released and handled, but I have to tell you that there has been a great deal of statistical information here that I believe to be very helpful to us.

I am grateful to you, General Chesney and to your staff for presenting the information to us this morning.

Thank you.

General CHESNEY. Thank you, sir.

Mr. APPLEGATE. Thank you, Mr. Daschle.

We also have with us the chairman of the Hospital and Health Care Subcommittee of the Veterans' Affairs Committee, Mr. Edgar of Pennsylvania.

Mr. EDGAR. Thank you, Mr. Chairman.

I apologize for not being able to be here for your full statement, but I had some other pressing business.

Could I ask just some very simple questions? Who was the person who made the decision to release the mortality study at this time?

General CHESNEY. We had promised this committee that we would do the study and release it as rapidly as we could.

Mr. EDGAR. Who made the decision to separate the mortality part from morbidity part, which is to be released later?

General CHESNEY. The decision was made on logistics reasons. It's easier to do the mortality study than the morbidity study and that's why it was done first. I think Colonel Lathrop made that decision, but it had to do with the ease of the study. There were fewer dead, they are easy to find, you can get good diagnoses. It's not 100th as hard to do the mortality study as it is the morbidity study.

Mr. EDGAR. Well, I share Congressman Daschle's feeling about the value of the information that you have shared in this report. I do have some concern about the way in which it was released because the average GI or veteran who has confronted me since this study has been released, reading the press reports of the study, make it sound that a conclusive decision has been made.

Yet, what I think I have heard you say in answer to previous questions is that these facts and figures should be held as a preliminary report at this time. Is that not correct?

General CHESNEY. That's correct. We said maybe 10 times in that press report that, "This is early, preliminary. It's the first thing we have. It's a baseline study from which our 20-year study will grow."

Mr. EDGAR. Your plan is to release the morbidity study in October?

General CHESNEY. Sometime during October if we can get it done and we are working very hard to do that right now.

Mr. EDGAR. What is the choreography for the release of that study? Are you going to do it the same way you did this release?

General CHESNEY. The decision on how to release the study was made out of the Secretary of the Air Force's office.

Mr. EDGAR. You state that a number of liver disorder deaths among Ranch Hand personnel is not statistically significant. Would you explain that, what you mean by "statistically significant"?

General CHESNEY. Statisticians use the laws of probability to determine if something is statistically significant. If it would happen only 5 times in a 100 or less, then it is considered statistically significant. If it happens 50 times in a 100 or 75 times in a 100, then it's not statistically significant. It's the 95 percent chance that this did not happen by chance that we determine that something is statistically significant.

Mr. EDGAR. In the entire study, did you have enough material to go on to make any clear observations in terms of statistically significant?

General CHESNEY. There was what, George, the deaths?

Colonel LATHROP. Yes, in the study we are only studying 1,247 individuals and certainly we have recognized that and heralded that in our particular study protocol. Notwithstanding, if there is marked case clustering, that is, if there is a marked excess of disease, in particular a rare disease like soft tissue sarcoma, it is theoretically possible to pick it up in a small study like this.

The Dow and Monsanto studies have clearly done this. That was one of our obligations, to do a mortality component to this effort.

To answer your question, the study is unlikely to detect rare diseases unless there is case clustering. It does have very remarkable strong power to pick up common conditions that we are looking at during the physical examination phase of the report.

Mr. EDGAR. You wouldn't as a result of this preliminary study that has statistical inconsistencies want to proclaim that the use of the defoliate in Vietnam was totally safe——

Colonel LATHROP. Absolutely not.

Mr. EDGAR. And that there was no impact from these?

Colonel LATHROP. Absolutely not. There are some very intriguing patterns that are beginning to emerge from this information, but again, only 4 percent of these people have died. Next year we anticipate that about 5 percent will have died. That's a 20 percent change in 1 year and could totally reverse the patterns that we are seeing as of the baseline. So it's going to be a matter of tracking this thing along and seeing what happens to the pattern.

Mr. EDGAR. And in those patterns that are troubling to you, what is the most troubling?

Colonel LATHROP. The less favorable mortality circumstance of the Ranch Hand enlisted because that conforms to their self-perception with regard to exposure.

Mr. EDGAR. Thank you. I have no further questions.

Mr. APPLEGATE. Thank you, Mr. Edgar.

I would like to make mention of a correction, General Chesney. You more or less inferred that you rushed this study out at the request of this subcommittee and I don't think that is correct.

General CHESNEY. Not the subcommittee, the full committee.

Mr. APPLEGATE. Well, I don't know that that is necessarily correct either. According to the chairman, that isn't true. But we had set the hearing up in conjunction with your release of the study and we were happy to do so.

Mr. MONTGOMERY. Would the chairman yield?

Mr. APPLEGATE. I certainly will.

Mr. MONTGOMERY. As I recall, what we did request is, "When can you give us this study? When will it be out," and the Air Force gave us the date of June and then we went with that date.

General CHESNEY. This study was first conceived in 1978 on the pressure of Congress and at least twice I have been here and have been beaten about the head as to, "Why do you not have it done today?" There has been a lot of pressure on that. So we have tried to do it and do it correctly, as quickly as we could.

Mr. MCEWEN. Would the chairman yield?

Mr. APPLEGATE. Yes.

Mr. MCEWEN. I think the general is absolutely correct. If you had this information and didn't release it, you can rest assured that you would probably be beat about the head again.

General CHESNEY. Yes, sir.

Mr. MCEWEN. So I am sure that repeatedly we have expressed the desire of this committee to get it at the earliest opportunity and I appreciate your doing so.

Mr. EDGAR. Would the gentleman yield?

Mr. MCEWEN. I would be glad to yield.

Mr. EDGAR. As one of the beaters about the head, I, too feel as though you were under a great deal of pressure from this committee to release the report and my series of questions related primarily to the reasons why it was divided in terms of not waiting until the total report was ready to release both the morbidity and the mortality aspects, but I share my colleague from Ohio's comments that we have put a great deal of pressure on the Air Force to get on with its study, to be serious about its study, to make sure its study was significantly done and statistically accurate and that the protocol met the requirements that this committee has laid out.

Just a final comment, consider this a beating about the head to get the results of the morbidity study. [Laughter.]

General CHESNEY. Thank you, sir.

Mr. APPLEGATE. Thank you, Mr. Edgar, Mr. McEwen.

Mr. Denny Smith, do you have some further questions?

Mr. DENNY SMITH. Yes, Mr. Chairman.

Mr. Spey, a couple of questions. How long was this chemical used in the civilian——

Mr. SPEY. Approximately 20 years, sir. And 2,4,5-T, I think, to correct the record, is still being used in range lands and rice crops.

Mr. DENNY SMITH. It is still being delivered by air virtually in the same manner that you handled it. You mentioned earlier that the chemical was delivered from—or to you people in the Ranch Hand operation in a concentrate form, I presume.

When you mixed it, what did you mix it with as a carrying agent?

Mr. SPEY. Herbicide Orange, or 2,4-D, 2,4,5-T. We did not mix it with a carrier, sir. It was sprayed right out of the drum.

Mr. DENNY SMITH. You did not dilute it.

In operation of the airplanes, it seems like my memory serves me that there was normally more than one airplane in a formation which would be somewhat wings overlapping sometimes and in-trail, part of time crossing behind and in the spray vapor. Right?

Mr. SPEY. The swath width of the aircraft was approximately 240 feet, depending on the nozzle arrangement. So between airplane centers we had a sizable distance. It wasn't unusual, however, if the leader made a turn too rapidly for you or something like that, the No. 2 or possibly the No. 3 aircraft would go through the wake turbulence of the preceding aircraft and your windshield went totally obscure and you looked for the nearest thunderstorm to get washed out in so you could see the land when you got home.

It was possible to reach your hand out—of course, you were finished, as far as the spray mission was concerned, without visibility. You could reach out very carefully with your hand, keeping your hand flush against the window and wipe off about a third of your windshield with a rag.

Mr. DENNY SMITH. But that wasn't unusual really was it, if you have looked at some of the airplanes.

Mr. SPEY. We tried to avoid it, obviously, because of the danger of the wake turbulence, as you are aware of. It was easy to lose control of the airplane, particularly at high angles of attack. But it was not unusual for it to occur.

Mr. DENNY SMITH. In the "Venturi Effect" you talk about you normally flew with the windows open for ventilation in the airplane?

Mr. SPEY. Yes, that's correct, sir. We were under no pressurization air conditioning except for the open windows, and we breathed the fumes from the spray tank, which was located in the center of the cargo compartment. We flew with the troop door open so that the flight engineer could mark the ground fire with colored smoke, and the air flowed from the aft forward and out through the cockpit and the side windows.

Mr. DENNY SMITH. OK. Thank you, Mr. Spey.

General, I guess I have to clarify a couple of things. What was the total number of people who were involved in the Ranch Hand operation?

General CHESNEY. 1,269 that we have been able to identify.

Mr. DENNY SMITH. 1,269. That's all the people that were ever assigned to Ranch Hand in any specific area where they dealt with this dioxin?

General **CHESNEY**. Yes, sir, as far as we can determine and we have gone through something like 15 million documents. There was a fire that destroyed a few documents in St. Louis, so there may have been a few more. We picked up six more this last year that we did not know were there, but that's a close number.

Mr. **DENNY SMITH**. And of the 1,269, the total number of deaths or mortality is what?

General **CHESNEY**. Fifty after they came home from Vietnam and 22, I think, in Vietnam. So 77, and there are two that we have never been able to find. They did not die in the United States. They may have gone to Bora Bora or someplace, but we have just been unable to find two Ranch Handers.

Mr. **DENNY SMITH**. So that's how you come to the 4 percent figure?

General **CHESNEY**. Yes, sir, 4 percent have died.

Mr. **DENNY SMITH**. OK. Have there been any studies done in private use of this chemical by agricultural interests in trying to delineate the problem?

General **CHESNEY**. There was a study done up in Tree Spring that I know of that looked primarily at the birth defects; it was not a good statistical study; it was collecting the numbers there and saying, "We have birth defects".

Are there any others, George?

Colonel **LATHROP**. No, sir. USDA was contemplating such a study among pesticide workers. There are also some railroad worker studies ongoing, I believe.

Mr. **DENNY SMITH**. OK. Thank you very much.

Thank you, Mr. Chairman.

Mr. **MONTGOMERY**. Would the gentleman yield?

Mr. **DENNY SMITH**. Sure. I would be happy to, Mr. Chairman.

Mr. **MONTGOMERY**. I will be very brief. I want to commend the gentleman. We are fortunate to have the knowledge that you have as a Vietnam veteran, who was in Vietnam and also Mr. Daschle who is a Vietnam veteran.

For the record, Mr. Chairman, I would like to say—and I put in the record a letter from the Environmental Protection Agency—but again I would like to repeat that on May 20, 1983, the Environmental Protection Agency says that "2,4,5-T is in use today on noncrop land, industrial sites, range land and rice fields." So it is still being used.

Mr. **APPLEGATE**. Thank you, Mr. Chairman and Mr. Smith.

The gentleman from Ohio, Mr. McEwen, has a unanimous consent request.

Mr. **MCEWEN**. Mr. Chairman, as to the Dow Chemical interoffice memos that were referred to by the Representative from Texas, it is my understanding attempts have been made to secure them by the Veterans' Administration. If the VA is successful, I would request unanimous consent that we request the Veterans' Administration to forward them to the committee for its report.

Mr. **APPLEGATE**. Without objection.

Mr. **EDGAR**. Mr. Chairman?

Mr. **APPLEGATE**. Mr. Edgar.

Mr. **EDGAR**. I would just like to ask unanimous consent that for the record I be permitted to inquire in some detail of the Air

Force—I have a list of specific questions I would like to share with them.[1]

General CHESNEY. I will be happy to take them for the record, sir.

Mr. APPLEGATE. Thank you, General.

Thank you very much for appearing before the committee. We appreciate your report and we look forward to seeing you again.

General CHESNEY. Thank you, sir.

Mr. APPLEGATE. We are indeed privileged to have with us one of our Nation's heroes, a winner of the Congressional Medal of Honor, Mr. Sammy Davis, who will testify at this time. Mr. Davis' good qualities, amongst other things, are that he was born in Ohio, and, unfortunately, moved to Illinois and that's where he lives now.

Is Mr. Davis in the room?

Mr. MONTGOMERY. Mr. Chairman, as Mr. Davis is coming up, one thing that concerns me is we have witnesses from the government who will testify and then they will all leave. I wish that some of the Ranch Hand study group would stay around in case there are other questions—at least one or two of them, but they all seem to have left.

Mr. APPLEGATE. Is there someone who would like to go out and retrieve one or two members of the Ranch Hand study group?

I think that's a good suggestion, Mr. Chairman, since this is the primary reason for our hearings today.

Mr. Davis, it's very good to have you here with us.

Mr. DAVIS. Thank you.

Mr. APPLEGATE. We look forward to hearing what you have to tell us.

Mr. DAVIS. Thank you, sir.

STATEMENT OF SAMMY DAVIS, CONGRESSIONAL MEDAL OF HONOR WINNER

Mr. DAVIS. I am a country boy and I was raised with a country boy's love for this Nation and the belief in what my Government was doing. In 1966 I joined hundreds of thousands of young men, who voluntarily enlisted in the Armed Forces because we were convinced America needed us to serve her—a step I would take again today without any hesitation.

On a November night in 1967, good fortune and determination delivered me from the most difficult set of circumstances and I was awarded the honor which I humbly display today.

Throughout the darkest night of my life, although there was no one immediately present at my side, I never for a moment doubted that America herself was standing next to me.

I come here today to join you once again standing alongside America seeking to serve her best interests.

Upon my discharge from the service in 1969, the state of my health began to lead me on a journey that, in many respects, is not unlike my travels through a jungle on the other side of the world. I have walked miles of hospital corridors while in pain, seeking the answers, fearing the worst, but pressing on because I believed it to be my duty to my family and myself. While there was always another prescription, additional speculation and what I believe to be a sincere effort to find the cause, the supreme question—why—could never be answered, and the pain could never be stopped.

---

[1] See p. 145.

The pain continues, the fear grows worse, but in March of this year I broke through the jungle into the light. One man, Dr. Bertram Carnow, was able to tell me what both he and I believed to be the cause of my suffering. While I have suspected for some time that agent orange and the dioxin contained in it may be responsible for the illnesses that have cost me nearly 4 years off in my time at work, 9 years of my employment, which I now must retire from, it was only Dr. Carnow who has been able to confirm that. I assure you that it is only my faith in Dr. Carnow, his confidence in his tests and ultimate diagnosis and not my suspicions, that are responsible for my belief in his opinion.

The diagnosis has given me both fright and relief. I know, and the doctor has confirmed, that I am not a healthy man. From my conversations with Dr. Carnow, I know that without the same good fortune that delivered me from the jungle 14 years ago, I may very soon be called away. I am 36-years-old, gentlemen, and that terrifies me. But at the very least, the darkness of uncertainty has passed and I can rest with the fact that I know what to expect now.

I did not travel the miles from West York, Ill., to the Capital to accuse anyone or any organization of any wrongdoing, indifference or malpractice of medicine.

Nonetheless, certain questions exist in my mind and in the minds of thousands of other Vietnam veterans. What can one doctor in Chicago do that the largest health care delivery system in the world cannot? What can one man examine, understand and diagnose that the largest health care system in the world cannot?

Can men who may not have years to wait for a completion of research be asked to stand by while there is a doctor who can answer their questions today? I submit, gentlemen, that we have a right to know, just as we did in Vietnam, why we may have to die.

I have come here today to win support for Congressman Daschle's legislation for two reasons. First, it will allow the Veterans' Administration to give immediate benefits to the men who are suffering, who cannot work, who can no longer feel the pride of making a contribution that they felt while they were in Vietnam.

Second, in the long run, approval of this legislation by Congress will be a definite, definitive signal to the Nation and the rest of the world that a problem does exist from exposure to agent orange, and that the greatest deliberative body the world has ever known wants to know about the problems. Beyond compensation, it will be a call for intensified research in both the public and private sectors into the damage this chemical has caused, the means to halt the damage and the way to a cure.

A great American hero, Lou Gehrig of the New York Yankees, once told a capacity crowd in a baseball stadium, in spite of the fact that he knew he was dying, he considered himself the luckiest man alive. Although I do not consider myself a hero, in light of the fact that Mr. Gehrig is no longer with us, I feel that I am now the luckiest man alive.

I have been blessed with a beautiful, loving wife who, in turn, has blessed me with three beautiful, healthy children I have also been given the rarest of opportunities in serving the greatest nation on the planet in a way few men are allowed to. I pray only that my family be allowed to grow and prosper in the same manner as I was, and I am left speechless when I consider the bounty that has befallen me.

Another man who was a hero, although perhaps only to me and the rest of his family, was my grandfather. When I returned from Vietnam he gave me a newspaper clipping that I still carry with me today. The clipping is a rendition of the last two stanzas of Lt. John McCrae's poem, "In Flanders' Fields". I would like to share some of the poem with the committee because he told me that it explained what serving in a war really meant.

> To you from failing hands we throw the torch; be it yours to hold high. If ye break with us who die, we shall not sleep, though poppies grow in Flanders' fields.

I am an American, gentlemen, and therefore too proud and too bull-headed to beg you. But I humbly request that you do not break faith with those of us who answered the call that came from this very building. Think of the legacy you will leave for the next army you may have to raise to stand under our flag should you turn your backs on us. I can only ask you to do what is right.

Thank you for allowing me the honor of being here today. I will now try to answer any questions.

[The prepared statement of Mr. Davis appears on p. 146.]

Mr. APPLEGATE. Mr. Davis, thank you very much.

Mr. Montgomery.

Mr. MONTGOMERY. Thank you, Mr. Chairman. I want to thank Mr. Davis for being here today and we certainly have always said that the bottom line is the Government doesn't have many obligations to its people. People have more obligation to the Government, except in one case and that's when a person like you is called upon to serve his country in time of distress, and you serve your Nation well. I believe I can safely say that that is why we are having these hearings, to find out the effect of agent orange. I might also add that this committee several years ago increased the compensation or pension for the Congressional Medal of Honor winners—we doubled that amount. It's not a lot, but we do care and we will continue to show an interest. I appreciate your testimony.

The only comment I would have or question—do you mainly go through the Veterans' Administration now? I think you have a service-connected back problem, is that correct?

Mr. DAVIS. Yes, sir.

Mr. MONTGOMERY. That's through the Veterans' Administration?

Mr. DAVIS. Yes, sir.

Mr. MONTGOMERY. Are you treated fairly there? Do you have any problems with the treatment or the compensation?

Mr. DAVIS. No, sir, the Veterans' Administration has been very nice, very understanding, although they cannot say anything about agent orange. Because I have spent so much time in the hospitals, I have struck up a reasonably casual relationship with the doctors and they have told me things that they could not publicly say because it would mean that someone would come down on them.

Mr. MONTGOMERY. Do you feel like you have a problem from agent orange that is physically affecting you?

Mr. DAVIS. Yes, sir; I do.

Mr. MONTGOMERY. What physical defect?

Mr. DAVIS. Well, sir, I have a report here. After I went through the agent orange screening, which I went through at Woods VA Hospital in Milwaukee, Wis., I was up there approximately 2-1/2 months. I let them do every examination that they wanted to do to try to determine why I felt the way I do, which is poorly.

After trying to convince me that I had muscular distrophy or multiple sclerosis and I kept telling them, "No, sir, I don't feel that this is what is wrong with me". The basis that I put this on was that when we dedicated the Vietnam Memorial that was the first opportunity that I had had to talk to a large amount of Vietnam veterans. I was in the 9th Infantry Division and we had our 9th Infantry Division reunion at that time. What was so startling about it, what opened my eyes to it was the fact that in our conversation, I said, "Well, I hurt here," which sounds strange, but we talked to 1,500 people and the amount of people that hurt exactly right here [indicating] or had headaches was phenomenal. The only thing that we had in common—we had bankers, lawyers, farmers, even Governors—the only thing that we did share was the fact that we did serve in Vietnam together and we all hurt in the same place. So that's when I decided, "Well, maybe I better go to a—" I thought I was the only one that hurt.

I had been plodding on as I could with my work. Like I said in the 9 years of my employment with the company that I now work with I have missed 4 years because of sickness. I am not a malingerer, sir. I have been very proud and I have worked very hard and this hurts my feelings that I cannot work, I can no longer function on a daily basis, and I feel that it is because of agent orange. I know that I was sprayed at least three times directly.

General Chesney said that he felt that his boys were more exposed to agent orange than the ground troops. Well, I was a ground troop and we lived in it 24 hours a day, sir. They sprayed it on our areas. They came in and said, "Well, now, we are going to spray this area, but it will go away. It gets absorbed and taken up by the atmosphere and stuff in about 2 weeks. So you don't have nothing to worry about." We go in and we sleep in it and we ate it and we drank the water. You put little pills in it to purify the water, but it doesn't do a thing to agent orange.

I think it just needs to be looked into a little bit deeper. You are kind of hitting the surface. You are not going down into the bottom of the well and finding out what the real problem is. This is my opinion.

Mr. MONTGOMERY. I have one other question and my time is up. It's showing up now that there are a number of psychological problems that we have seen more in the Vietnam veteran. Can you classify the psychological problems that this committee should be concerned about on the agent orange issue?

Mr. DAVIS. Well, sir, I feel that agent orange does cause some psychological problems. There is organic brain damage caused by agent orange. I have here Dr. Carnow's report and I will read you what he found after the VA gave me a clean bill of health.

Mr. **Montgomery**. We asked him to testify at this subcommittee and he turned us down.

Mr. **Davis**. Yes, sir, I realize that. I don't know why. He is a very busy man, a very dedicated clinician.

Mr. **Montgomery**. Go ahead.

Mr. **Davis**. OK.

The diagnosis. First there is chronic, chemical intoxication from dioxin 2,4,5-T and 2/4-D. No. 2, probable damage to the central nervous system with petit mal-type seizures, severe anxiety and moderate to severe depression.

No. 3, peripheral neuropathy, secondary to number one, which is chronic chemical intoxication. Number four, lipid metabolism derangement, secondary to chemical damage to the liver, secondary to number one; conjuctivitis, secondary to number one; possible damage to reproductive organs, secondary to number one; hypertension secondary to number one; coronary insufficiency with possible myocardiopathy, secondary to number one; polyarthralgia, secondary to number one; muscle spasm and muscle weakness, secondary to number one; chronic gastritis and chronic enterocolitis, possible secondary to number one.

Dr. Carnow has been the only doctor—I know that I hurt; the other Vietnam veterans know that they are hurting. They go to doctors and the doctors can find no reason for them to hurt. Dr. Carnow has been the only doctor that has the cause and relation between agent orange and our health problems.

Mr. **Montgomery**. Thank you. I have gone way over my time.

Thank you. You have been most helpful.

Mr. **Applegate**. Thank you, Mr. Montgomery.

Mr. Denny Smith.

Mr. **Denny Smith**. Mr. Chairman, thank you.

Mr. Davis, it's a real pleasure to have you before the committee today and I just ask unanimous consent that your record and your citation of your activities be entered into the record.

Mr. Chairman, do you suppose we could do that, if there is no objection?

Mr. **Applegate**. I don't see why not. Without objection it shall be.

[The information follows:]

Davis, Sammy L.

Rank and organization; Sergeant, U.S. Army, Battery C, 2d Battalion, 4th Artillery, 9th Infantry Division. *Place and date:* West of Cai Lay, Republic of Vietnam, 18 November 1967. *Entered service at:* Indianapolis, Ind. *Born:* 1 November 1946, Dayton, Ohio. *Citation:* For conspicuous gallantry and intrepidity in action at the risk of his life and beyond the call of duty, Sgt. Davis (then Pfc distinguished himself during the early morning hours while serving as a cannoneer with Battery C, at a remote fire support base. At approximately 0200 hours, the fire support base was under heavy enemy mortar attack. Simultaneously, an estimated reinforced Viet Cong battalion launched a fierce ground assault upon the fire support base. The attacking enemy drove to within 25 meters of the friendly positions. Only a river separated the Viet Cong from the fire support base. Detecting a nearby enemy position, Sgt. Davis seized a machinegun and provided covering fire for his guncrew, as they attempted to bring direct artillery fire on the enemy. Despite his efforts, an enemy recoilless rifle round scored a direct hit upon the artillery piece. The resultant blast hurled the guncrew from their weapon and blew Sgt. Davis into a foxhole. He struggled to his feet and returned to the howitzer, which was burning furiously. Ignoring repeated warnings to seek cover, Sgt. Davis rammed a shell into the gun. Disregarding a withering hail of enemy fire directed against his position, he aimed and fired the howitzer which rolled backward, knocking Sgt. Davis violently to the ground. Undaunted, he returned to the weapon to fire again when an enemy mortar round exploded within 20 meters of his position, injuring him painfully. Nevertheless, Sgt. Davis loaded the artillery piece, aimed and fired. Again he was knocked down by the recoil. In complete disregard for his safety, Sgt. Davis loaded and fired 3 more shells into the enemy. Disregarding his extensive injuries and his inability to swim, Sgt. Davis picked up an air mattress and struck out across the deep river to rescue 3 wounded comrades on the far side. Upon reaching the 3 wounded men, he stood upright and fired into the dense vegetation to prevent the Viet Cong from advancing. While the most seriously wounded soldier was helped across the river, Sgt. Davis protected the 2 remaining casualties until he could pull them across the river to the fire support base. Though suffering from painful wounds, he refused medical attention, joining another howitzer crew which fired at the large Viet Cong force until it broke contact and fled. Sgt. Davis' extraordinary heroism, at the risk of his life, are in keeping with the highest traditions of the military service and reflect great credit upon himself and the U.S. Army.

Mr. EDGAR. Mr. Chairman.

Mr. APPLEGATE. Yes.

Mr. EDGAR. Will the gentleman yield?

Mr. DENNY SMITH. Yes, for just a minute.

Mr. EDGAR. I wonder, if under unanimous consent, we could also put the shopping list of symptoms that Mr. Davis has just described.

Mr. DENNY SMITH. Well, it's already been included in the record here. I think it's important that we know what he achieved and why he was so honored. So I think that's not necessary, Mr. Edgar.

Mr. EDGAR. Well, I ask unanimous consent that the statement of Dr. Carnow be included in the record at this point.

[The information appears on p. 150.]

Mr. DENNY SMITH. If I could reclaim my time, would you mind if Dr. Carnow's full report was given to this committee and, in turn, to the Veterans Administration?

Mr. DAVIS. No, sir, if it will help, you are more than welcome to it.

Mr. DENNY SMITH. Well, I think that's very important.

In your dealing with the VA hospitals, you mentioned the fact that the doctors were not able to talk about agent orange. It's my understanding that the doctors have been directed to look for anything that would be strange in nature that they should be trying to identify. Weren't they attempting that when they gave you a physical at—which hospital was it?

Mr. DAVIS. Woods.

Mr. DENNY SMITH. The Woods Hospital in Milwaukee, Wis.?

Mr. DAVIS. Yes, sir.

Mr. DENNY SMITH. Weren't they looking for symptoms that were unusual, that were not tied in to some other disease?

Mr. DAVIS. Yes, sir; they were looking for it.

Mr. DENNY SMITH. And did they talk about agent orange in trying to look for that?

Mr. DAVIS. Yes, sir; they did. They found no connection at all with my physical problems and agent orange.

Mr. DENNY SMITH. Well, you know, I think that the committee does have a real commitment to try and do what you asked for in your closing statement, that is, "to try and do what is right" for the veterans in this country and for all of the citizens, and that's why this hearing is important and why it is important that we have your testimony.

I don't know if you have ever been to Albany, Oreg., but each year on Veterans Day we do honor all of the Medal of Honor winners and there is a national gathering of those who are so honored.

We would be very pleased to have you come out to Albany and it's quite a nice recognition of what you did for this Nation. I would certainly hope that you could come out there and I will see to it that we get you an invitation.

I am really interested in what the VA has done for you. You feel that you have been well treated and they have looked for the cause. If Dr. Carnow is unwilling, as the chairman said, to come testify here at least his report will be a comparison. I wonder, has the Veterans' Administration system received his report?

Mr. DAVIS. Yes, sir; they have looked at it.

Mr. DENNY SMITH. And what was their feeling after they looked at that?

Mr. DAVIS. They scratched their heads and said, "Well, we don't understand."

Mr. DENNY SMITH. Do you think they were being less than honest or less than direct in trying to examine what, as you call him, a dedicated clinician, has arrived at?

Mr. DAVIS. I feel that they were doing all that they were allowed to do.

Mr. DENNY SMITH. All that they were allowed to do.

Do you feel that the Veterans' Administration is not prosecuting the agent orange issue as well as they should be, even though in your instance you feel like they have given you a good physical?

Mr. DAVIS. That's a very hard question to answer. All I can base it on is what I have been exposed to. The doctors that I have been associated with in the VA are concerned with the agent orange problem, definitely. They are aware that there is a problem. They are extremely cautious to say that any medical problem that I may have could be related to agent orange.

Mr. DENNY SMITH. Did Dr. Carnow do basically the same tests that the Veterans' Administration did?

Mr. DAVIS. Yes, sir.

Mr. DENNY SMITH. But his findings were different.

It would be interesting, Mr. Chairman, if we could have those two compared by someone in the Veterans' Administration or by others because, obviously, we have two different approaches and findings. I certainly relate to what you had to say earlier, Mr. Davis, about the fact that you don't know anything but what you feel, and those of us who served in Vietnam certainly are concerned about this problem.

But as you look at this Ranch Hand study that—and this is only on mortality at this point—statistically I think that it's pretty clear that we don't have the evidence to do anything other than what is being done, and that's to continue to study the problem.

I just wonder whether you would respond to that.

Mr. DAVIS. That is one of the problems. There's death and there are many things worse than death—to be a family man and not be able to provide for your family is worse than death, to be in pain constantly and to have no reasonable explanation. To many that is worse than death. To be robbed of the dignity that health has, that is worse than death.

Mr. DENNY SMITH. I don't doubt that at all, Mr. Davis, but the Veterans' Administration is providing some disability to you, is it not?

Mr. **Davis**. It's because I was shot in the back and shot in the leg; yes, sir. Those are visible defects that I have.

Mr. **Denny Smith**. So from that standpoint, you feel like the Veterans' Administration has been fair in that also?

Mr. **Davis**. Oh, yes, sir; definitely.

I don't have any complaint at all with the VA with the treatment that I have received. No, sir; I would say that I have some very good friends in the VA.

Mr. **Denny Smith**. Well, I am pleased to hear that and I appreciate your testimony. My time is up. Mr. Chairman, thank you.

Mr. **Applegate**. Thank you, Mr. Smith.

The gentleman from Texas, Mr. Hall.

Mr. **Hall**. Thank you, Mr. Chairman.

Thank you, Mr. Davis, for a very moving statement.

I would like to just touch on one or two things, if I might. How many times, and you may have said this and it slipped my mind, how many times did you say that you were involved in the agent orange process? Two or three times?

Mr. **Davis**. As close as I can recall, I can remember three times specifically that I was sprayed with agent orange. One time it blinded me for almost 2 days.

Mr. **Hall**. Well, was anyone else in the company that you were in that also was blinded?

Mr. **Davis**. I was the only one that was foolish enough to look up at the helicopter because it was coming in very low and very fast and I looked up just as he came over and I received a dose of it in my face and eyes.

Mr. **Hall**. By the way, were you an officer or an enlisted man?

Mr. **Davis**. No, sir, I was a private.

Mr. **Hall**. Did anyone instruct you not to look up at the helicopters that came in to make this pass?

Mr. **Davis**. No, sir, I should have had enough commonsense not to, but it was just the surprise of it coming in very low.

Mr. **Hall**. Well, how long was your uniform covered with this substance?

Mr. **Davis**. About a year.

Mr. **Hall**. The same uniform?

Mr. **Davis**. Well, I think I had a couple of changes, but you go out for 2 or 3 days—they tell you, "2 or 3 days" and you end up to be out for a week or 2 weeks and you wear the same uniform or same pair of boots.

Mr. **Hall**. You didn't wear the same uniform for a year, did you?

Mr. **Davis**. Almost. We try to get as much wear and tear out of them as we can.

Mr. **Hall**. All right.

During the time that you were on active duty and before you received the wounds from which, I am sure, you were discharged or thereafter——

Mr. **Davis**. No, sir, I wasn't.

Mr. **Hall**. All right. Did you ever have any problems of any kind while you were still on active duty with this inundation of agent orange?

Mr. **Davis**. Yes, sir, at the time, I did, but I didn't realize the connection. I had little white blisters mostly on my upper torso and arms while still in Vietnam, severe headaches. I had runny sores on my head and my ears.

Mr. HALL. Did any of the others who were in your outfit have the same symptoms?

Mr. DAVIS. Yes, sir.

Mr. HALL. Are any of those people still alive today?

Mr. DAVIS. Yes, sir.

Mr. HALL. Do you keep in touch with them?

Mr. DAVIS. I only know where two or three are.

Mr. HALL. Are they having the same symptoms that you are?

Mr. DAVIS. Yes, sir.

Mr. HALL. Have they been to their doctors?

Mr. DAVIS. I have tried to get them to go into the VA and they are still running scared from the fact that they don't want to admit that they are hurting.

Mr. HALL. Well, those men that you are talking about, are they working at gainful employment?

Mr. DAVIS. Yes, sir.

Mr. HALL. Your doctor, is he a general practitioner or is he a surgeon or is he an orthopedic man? What's his discipline?

Mr. DAVIS. I believe he is a toxicologist, sir.

Mr. HALL. Toxicologist?

Mr. DAVIS. Yes.

Mr. HALL. Do you know where he went to school?

Mr. DAVIS. I do not have with me his curriculum vitae but he is—the reason why we chose——

Mr. HALL. That's not important.

Have you ever, prior to the agent orange publicity that has been received in the past year or so—have you ever told a Veterans' Administration doctor that you feel that the amount of this substance that you got on you in Vietnam is the root cause of your problem?

Mr. DAVIS. Yes, sir.

Mr. HALL. Have they examined you thoroughly at all of the places you have been in hospitals trying to determine whether or not agent orange is a problem that you have today?

Mr. DAVIS. They examined me thoroughly, yes.

Mr. HALL. Have they told you that they can find no causal connection between what you have and agent orange?

Mr. DAVIS. Yes, sir, that's correct.

Mr. HALL. You have read these articles about the Dow Chemical that we have mentioned here today where they had some problems with it back in the sixties.

Mr. DAVIS. Yes.

Mr. HALL. Did anyone when you were in Vietnam ever have any comment to you about the probability that agent orange could be dangerous to the health of the soldiers?

Mr. DAVIS. No, sir, I can't remember anyone saying anything about agent orange. It was a Godsend to us being in the 9th Infantry Division because it allowed us to see what we were fighting. Without agent orange you couldn't see because of the foliage.

Mr. HALL. Well, did a big portion of this agent orange drip on down to the ground?

Mr. DAVIS. Yes, sir.

Mr. HALL. We have heard some comments here today that only about 10 percent of that substance ever got down to the ground level. Is that an accurate statement?

Mr. DAVIS. I don't feel it would be, no, sir, due to the fact that you could see it. I was in the delta where there is a lot of water and almost always you could see the blue rainbow film that it left on the water, but, like I said, nobody had said anything about it harming us so we drank it, we slept in the same mudhole that it was standing in——

Mr. HALL. Thank you very much for your testimony. My time has expired.

Mr. APPLEGATE. Thank you, Mr. Hall.

The gentleman from South Dakota, Mr. Daschle.

Mr. DASCHLE. Sammy Lee, I want to join with all of those on the committee who were privileged enough to hear your testimony this morning. I think it takes a lot of courage, which, obviously you have demonstrated in the past, to come before a committee and to relate your personal experiences and talk with the same kind of authority of prior witnesses who have come before this committee and talked. You did our committee a real service and I know that I speak for all of them in articulating our gratitude to you.

Let me ask you this: When you were having those problems, were they ever recorded on any of your medical forms?

Mr. DAVIS. The skin condition that I had should have been, but we were a very remote-type unit and our medic took care of almost all of our ills except for gunshots, and obvious wounds, and skin condition or runny sores on your head was the least of your problems. So I don't know if the record was ever written down

Mr. DASCHLE. So you could have easily been discharged and there wouldn't have been any kind of a recorded notation that you had experienced some serious sores all over your body. Is that correct?

Mr. DAVIS. Right.

Mr. DASCHLE. And you say that this is probably not uncommon, that others who were side by side with you had similar types of sores, who were probably exposed and those sores, too, were not recorded?

Mr. DAVIS. It was just kind of a joke among us, "Well, we have got the jungle rot." But the big, runny sores were constant almost the whole time that we served in Vietnam and, as far as I know, it was never entered on my medical record and I am sure it wasn't on the others.

Mr. DASCHLE. Let me ask you this, from the first time that you were sprayed to the third time, how long a period of time was that?

Mr. DAVIS. The first time that I was sprayed I think I had been in the country 5 or 6 days and I was at Bearcat, which was the 9th Infantry Division Headquarters, and they took us out for our Vietnam orientation, which consisted of issuing us an M-16 and two clips of ammunition, and we walked on the outside of the berm and fired the two clips of ammunition, the 40 rounds of ammunition. That was our Vietnam orientation. That made us expert jungle fighters. But while we were there—evidently the sergeant that took us out hadn't told anybody that he was going to take us out—there were about 60 of us, I believe, and that's when the helicopter flew over and effectively blinded me for almost 2 days.

Mr. **Daschle**. That was the first time. And how far into your duty was the last time? Three months? Six months?

Mr. **Davis**. I got there in March 1967. November 1968 was about the last time that I can remember being directly exposed to it.

Mr. **Daschle**. So as far as your direct exposure goes it went for more than a year?

Mr. **Davis**. Almost, yes, sir.

Mr. **Daschle**. From April 1967 to November 1968. So about a year and a half.

Mr. **Davis**. After I was wounded, I didn't have to go out into the field.

Mr. **Daschle**. And during that time of exposure, was the condition of your clothing such that, as I perceive it, that it was actually wet? How would you describe your clothing as you were sprayed?

Mr. **Davis**. Yes.

Mr. **Denny Smith**. Would the gentleman yield for just a second? Let me clarify one thing here. You entered the country when, and when did you leave the country? Normally a year tour was common.

Mr. **Davis**. March 7, 1967, to March 7, 1968.

Mr. **Denny Smith**. So you were saying November 1967 rather than November 1968?

Mr. **Davis**. Yes; pardon me.

In walking through the jungle, the vegetation was very heavy and it would be—you could see the little droplets. I can remember distinctly, like I say, the rainbows and we thought it was very pretty. But it would get on your clothing and you would have to wear that clothing without changing or showering or anything for weeks possibly before you actually get in and put clean clothing on. Sure, you would wash them out if they got dirty. You could take them off and wash them out in a mudhole, but that very same mudhole was just as contaminated as the foliage was.

Mr. **Daschle**. Well, I could go on and on, I guess, but after hearing testimony of that kind, it just seems to me that it's imperative that we recognize that, while there still may be questions out there, there may never be that causal relationship that we seek, even if we spend $100 million rather than—or I should say $100 billion, whatever the amount, we may never get, with finality, what we are looking for. But to give the Sammy Lee Davis' the benefit of the doubt seems only to be what you are asking for and I commend you for coming before the committee to make the case as well as you have.

Mr. **Davis**. Thank you, sir.

Mr. **Applegate**. Thank you, Mr. Daschle.

Mr. Edgar.

Mr. **Edgar**. Thank you Mr. Chairman. Mr. Davis, I want to thank you for sharing from a very personal perspective your personal story. When Congressman Smith asked that your heroic record be included into the record of these hearings, I was very pleased to join that, but I wanted to include with that your medical record as well, because I think that the symptoms of your heroism, as important as they are, also need to be matched with the symptoms of your medical record so that we can try to respond to that in a specific way.

The doctor that examined you that you have been citing in the testimony today put in technical, medical language the symptoms, but I wonder if you could just briefly describe for the committee your symptom history from your discharge to the present, in your language and how you feel.

Mr. **Davis**. Yes, sir.

When I first got out of the service, I had nausea, I was sick to my stomach frequently, headaches. For about 2 years I still had the white blisters appear, mostly in the summertime. In the wintertime it would basically go away. I would only be put out of commission, healthwise, maybe 2 or 3 days out of the month, which wasn't too bad. I would run fevers, chills, cold sweats, but that was almost 15 years ago.

Now it has progressively gotten worse. Now I feel good maybe 2 days out of a week and for the remainder I am down—weakness in the legs, extremities, which is very confusing. I have always been a strong man and to not be able to get on the end of a shovel and do a good day's work is very aggravating to me.

Go ahead, sir, I forgot the question.

Mr. **Edgar**. Well, I was asking about symptoms and you made a statement in your testimony that you felt your health had deteriorated to the point where you would have to retire from your position. What kinds of symptoms are demonstrated that would cause you not to be able to at least hold part-time work? What are the kinds of conditions that you are experiencing personally?

Mr. **Davis**. I have angina, which is heart pain, coronary insufficiency, I get very dizzy, I have petit mal seizures, muscle weakness, the weakness in the legs and the arms. I asked Dr. Carnow to explain it to me why I got so weak and he said, "Well, it's like—" he broke it down very simple for me. He said, "It's like having a 427 racing engine and a pint a gas. You can idle all day or you can give her one burst and you're done." That's very true. If I take it very easy, sit around and stuff, I can be up all day, but if I try to do anything, walk up a set of stairs or something, it exhausts me to the point that I get very ill.

Mr. **Edgar**. Thank you. I appreciate your sharing those symptoms and specifics with us of your own medical history because I think that will be helpful for the record.

Mr. **Davis**. Yes, sir.

Mr. **Edgar**. Mr. Chairman, I have no further questions.

Mr. **Applegate**. Thank you very much, Mr. Edgar.

Mr. Davis, thank you again very much for appearing before the committee. We appreciate your comments and your statement.

Mr. **Davis**. Thank you very much for the opportunity to let me serve you.

Mr. **Applegate**. Our next witness is Dr. John R. Beljan, provost and senior vice president, Wright State University, Dayton, Ohio, representing the American Medical Association.

Dr. Beljan, I might mention to you that Congressman Bob McEwen, the ranking minority member had to leave because he had another commitment and so he asked that you forgive his absence.

Dr. **Beljan**. I am delighted to know that it isn't because of my testimony that he is leaving.

Mr. APPLEGATE. I am sure that it isn't.

If you would be so kind as to introduce those who are accompaning you. I understand that you have a prepared statement, which will be entered into the record in its entirety. You may summarize your statement if you so desire.

STATEMENT OF DR. J. R. BELJAN, SENIOR VICE PRESIDENT OF WRIGHT STATE UNIVERSITY, DAYTON, OHIO, REPRESENTING THE AMERICAN MEDICAL ASSOCIATION, ACCOMPANIED BY LEONARD D. FENNINGER, M.D., VICE PRESIDENT FOR MEDICAL EDUCATION AND SCIENTIFIC POLICY, AMERICAN MEDICAL ASSOCIATION; AND HARRY N. PETERSON, DIRECTOR OF THE DIVISION OF LEGISLATIVE ACTIVITIES, AMERICAN MEDICAL ASSOCIATION

Dr. BELJAN. Thank you, Mr. Chairman. I very much appreciate the opportunity to be here to speak on behalf of the American Medical Association and to compliment your committee on its important work in trying to ferret out the answers to a very difficult problem.

My name is John R. Beljan, M.D., and I am currently senior vice president of Wright State University in Dayton, Ohio, and was the founding dean of its school of medicine. I am currently a member of the Council on Scientific Affairs of the American Medical Association and I served as chairman of the Association's Advisory Panel on Toxic Substances that prepared the AMA's 1981 report on "Agent Orange and Dioxin Contamination."

I believe your subcommittee, Mr. Chairman, has received a copy of this report.

Accompanying me, to my left, is Dr. Leonard Fenninger, AMA's vice president for Medical Education and Scientific Policy and to my right, Mr. Harry N. Peterson, director of the Association's Division of Legislative Activities.

We are pleased, Mr. Chairman, to accept your invitation to appear today to discuss AMA's view concerning the human health effects of exposure to the toxin TCDD.

This subject is particularly important in light of the legislation currently before this subcommittee.

In 1981, the AMA House of Delegates adopted a report entitled "The Health Effects of Agent Orange and Polychlorinated Dioxin Contaminants." [1] Copies of this report were submitted to your committee with our formal statement. This report was developed by the Association's Council on Scientific Affairs and was based on the investigation of its select panel on toxic substances of which I was chairman.

This report was initiated because of concern about the reported adverse health effects to humans from exposure to agent orange during the Vietnam conflict. Medical complaints—and we heard a number of them just previously—noted by veterans included weight loss, liver damage, recurrent skin rashes, deformed offspring, stillbirths, cancer, sterility, personality changes and other illnesses.

---

[1] See p. 163.

This report, however, was not limited to studies involving exposure of U.S. Forces to agent orange, but, indeed, included the review of all reported exposures during the last four decades.

The dioxin TCDD was present in agent orange, as you well know, as a byproduct of its manufacture. The AMA report on dioxin was an examination of the then available current information published in the open literature on the effects of the substance on animals and human health. This study by our expert panel was a major undertaking, given the very substantial amount of literature reporting experience with animal and human populations that has been generated over the past four decades.

The report states, and I quote, "TCDD by itself is extremely toxic; along with botulinus bacillus toxin and aflatoxin, it is one of the most lethal organic chemical compounds known to man." The report recognizes and describes the toxicity of TCDD, pointing out the varying toxicity among different animal species and the relationship between toxicity and the amount and type of exposure and ingress to the body. This position, formulated in 1981, remains and is still the policy of the AMA.

The report concludes that of the suggested adverse health effects on human beings attributed to dioxin exposure, there is conclusive evidence of a cause-and-effect relationship only with respect to chloracne. Chloracne is a not uncommon form of occupational dermatitis and may also be caused by other chemical agents. It usually clears within several months of exposure, although severe chloracne may be persistent and has been known to last for as long as 15 years following cessation of exposure to the causal agent.

With respect to other suggested human health effects attributed to dioxin or TCDD, the Council on Scientific Affairs and its advisory panel concluded that there was insufficient published data subject to peer review to establish a relationship between dioxin exposure and the adverse health effects suggested.

The report reviews in detail the published scientific literature that supports these conclusions. I would also note that the report of the Congressional Research Service of the Library of Congress entitled, "Dioxin: Environmental Impacts and Potential Human Health Effects," published June 6, 1983, surveys the body of scientific opinion in its conclusion. This survey is consonant with the 1981 AMA report.

Mr. Chairman, the AMA has a continuing obligation to promote the public health in matters such as this and to inform the profession and the public of the most current information. We note that this matter is not static and that new evidence will be reviewed as it becomes available.

Therefore, we do not intend to let this important matter drop. Action taken by the House of Delegates calls for an updating of our report on agent orange and dioxin this year along with an active program to provide the public the most accurate information available on dioxin. The new literature is scheduled to be reviewed by our expert panel next month. The findings are expected to be presented to the AMA Board of Trustees in October, with consideration by the House of Delegates at its meeting in December.

We will inform you of our conclusions.

Mr. Chairman, we would be happy to answer any questions that the subcommittee may have.

Thank you.

[The prepared statement of Dr. Beljan appears on p. 159.]

Mr. **Applegate**. Thank you very much, Dr. Beljan. We appreciate your being with us this morning sharing your expertise with us.

Mr. Daschle.

Mr. **Daschle**. Dr. Beljan, I was pleased to see the reports of your testimony before another committee in Congress—I don't have the name of the subcommittee in front of me right now—a couple of weeks ago because I understand that it clarified the position of the AMA with regard to dioxin, that, indeed, you do consider dioxin a serious health hazard. Is that correct?

Dr. **Beljan**. We consider it a serious public health problem and it is certainly a potent toxic agent in animals.

Mr. **Daschle**. You suggest on page 3 of your testimony, "Of the adverse health effects on human beings attributed to dioxin exposure, there is conclusive evidence of a cause and effect relationship only with respect to chloracne."

How do you look upon other kinds of diseases in which higher incidences of those diseases can be shown due to exposure? Do you not attribute that to be a higher health hazard when higher incidences can be shown, even though a causal relationship cannot?

Dr. **Beljan**. I think we have to be convinced that there are evidences of clustering and increased incidences and that the alleged agent under question has not been involved with a variety of other possible confusing factors as well. So the answer to your question is: If you could do the examination in isolation in a laboratory environment, I think we could conclusively answer yes or no.

Mr. **Daschle**. In other words, if you could do it on humans, you probably would be able to derive a much better appreciation of not only the higher incidences of these diseases, but also a causal relationship.

Dr. **Beljan**. That's not necessarily true and we would prefer, of course, not to use humans as experimental subjects.

Mr. **Daschle**. So, obviously, then you are only allowed—within the confines of proper study, obviously, you can't use the human subjects and so you are confined then to animals.

Where we see increases in various diseases within animals, for our purposes in compensation, in treating veterans who are experiencing many of the same diseases shown to be experienced in animals under laboratory conditions, would it not then be a reasonable expectation to want to treat and compensate veterans for those diseases?

Dr. **Beljan**. Let me not conjecture about compensability. I believe that that's the proper function of Congress. Let me speak to the scientific aspects that you posed to me. First of all, there is human experience, inadvertent human experience—several industrial exposures in which populations were sprayed with dioxin—in which careful followup has failed to show clustering, increased incidences of diseases and so forth. So there is a broad base of human experience that has been inadvertently caused by industrial accidents or industrial exposure.

Second, one cannot make direct extrapolations from animals to man. There is no appropriate animal model for dioxin. Unfortunately, even within experimental animal members of the same family of animals react very differently. This agent is extremely lethal, for example, to guinea pigs, and yet, other members of that same animal family are 5,000 times more resistant.

I would point out that we have had the same kinds of concerns about trying to make relationships in man from human models. Our recent problem with saccharin, for example, is a very good example; there is animal experience which does show it to be a toxic agent. I am sure that if we were to do the experiment in man, which I would not recommend—ingestion experiments and other kinds of things—that we may well see the data. But in those which have already been inadvertently done, we have, in careful examination of those studies, not found the causal relationship that would assist you in making the kinds of decisions that you, as a congressional body would wish to make.

Mr. **Daschle**. I am troubled a little bit. I mean, the AMA states as its purpose, obviously, advancing the cause of medicine for man. Now if you have two situations in animal testing, one that shows it's a very toxic and probably a lethal chemical for certain animals—Mr. Chairman, would you mind if I had 2 additional minutes?

Mr. **Applegate**. Go right ahead.

Mr. **Daschle**. On the other hand, you have evidence where in other animals it was not toxic, maybe not lethal. It seems as if the AMA is telling us that "We are going to assume that for man it's not lethal, that it's not toxic until we can be shown that it is."

It seems to me that that is turned around. I mean, if you really are concerned about the health and well-being of human beings and you can be shown that in certain laboratory animals it is toxic, it is lethal, why is it that you are not making the assumption that in humans it is until it is proven that it isn't? It seems to me that you are jeopardizing the health and well-being of human beings by making that very paralyzing assumption.

Dr. **Beljan**. I appreciate your statement although I would not, of course, support it. I believe that we are concerned with human health.

Mr. **Daschle**. Substantiate that for me. Why, given those two conditions, would you be willing to jeopardize the health of human beings, knowing that in some cases it does kill animals.

Dr. **Beljan**. Let me say that the AMA is not alone in this position, that other bodies——

Mr. **Daschle**. Well, I don't have other groups here. I am talking to the AMA right now. Why does the AMA feel that, even though we know it's lethal to certain animals—why are you willing to assume that it is not for humans?

Dr. **Beljan**. Because of the body of evidence on the other side which shows extensive experience with humans has failed to show convincing evidence of its danger.

Mr. **Daschle**. Convincing to whom?

Dr. **Beljan**. That is a fact, sir.

Mr. **Daschle**. Convincing to whom?

Dr. **Beljan**. Convincing to the medical and scientific community who are critically reviewing this data in terms of facts and conclusions that can be drawn.

I would point out, sir, that this agent, a defoliant, has been used for 30 years in the United States, that your concern should then reflect what has happened in that 30 years of exposure. There have been a series of studies done which looked at experience in Oregon and elsewhere regarding its use in agricultural applications. The Scientific Advisory Committee on Pesticides in the United Kingdom has looked at all of this data and has not restricted the use of this defoliant in the United Kingdom.

So I would suggest humbly, sir, that the data does not support a conclusion that this agent creates ravaging effects in man. It has been shown clearly, however, that chloracne is one of the agents in which there is a definite causal relationship.

Mr. **Daschle**. Well, I think you certainly don't share the view expressed by many other scientists who would just flatly contradict what you have just said, and I really have trouble understanding——

Dr. **Beljan**. I would be delighted to have that information.

Mr. **Daschle**. I have trouble understanding, why, if it can be shown that it is that toxic, that lethal in certain animals, you are unwilling to extend the same benefit of the doubt to human beings until it can be proven conclusively that it is not harmful. We had to live with 200 years of tobacco smoking—200 years in this country, who knows how long prior to that—before it could be shown in this case that tobacco was harmful. I would hope that, as we go through this, that we would at least give the benefit of the doubt to human beings when it comes to the recognition of the relationship between toxicity and ultimate medical problems.

Thank you, Mr. Chairman.

Dr. **Beljan**. I would like to ask Congressman Daschle the names of the organizations and the data that he has described because we would like to review that.

Mr. **Daschle**. Come with me to my office. I would love to give you an entire library full of information and you're welcome to join me in my research at any time because it's there and rather than give it to you off the cuff, I would rather give it to you in complete detail.

Dr. **Beljan**. Well, I would appreciate that, sir, and let me suggest that our panel will be delighted to review it and to subject it to the critical scientific review that it demands.

Mr. **Daschle**. Well, I would hope so and I would hope that you would consider the qualifications of those who are reviewing. I don't consider an ophthalmologist an expert on toxicity which is what we had in the case of your resolution.

Dr. **Beljan**. Let me make the matter clear because there appears to be some confusion. Our ophthalmologist was not a member of the review panel that looked at and studied the published literature available to us.

Mr. **Daschle**. Who was the sponsor of the resolution? Was the ophthalmologist the sponsor of the resolution?

Dr. **Beljan**. The Missouri delegation was the sponsor of the resolution, but our report antidated that resolution. On the scientific panel that reviewed the world literature available to us were a variety of people who reflected the scientific expertise available, some of whom were not AMA members.

Mr. **Daschle**. But the ophthalmologist certainly was the author of the resolution from what accounts I have read. Is that not correct?

Dr. **Beljan**. I do not know that, sir. I know that he spoke to the resolution. I know that he is personally concerned about it. He is a newly elected member of the Council on Scientific Affairs, but that is postdating the action of the council.

Mr. **Applegate**. Thank you very much.

Mr. Edgar.

Mr. **Edgar**. Thank you, Mr. Chairman.

Let me just make a couple of things clear. You are testifying today on the resolution and on the study that the AMA has done. To be clear for the record, the study is a review of literature. You are not going into the laboratory and doing original testing yourself?

Dr. **Beljan**. That is correct. We are reviewing all of the information related to dioxin available to us in the open literature.

Mr. **Edgar**. So your experts are reading page after page of factual evidence and literature documents. Is that correct?

Dr. **Beljan**. That is correct.

Mr. **Edgar**. Let me try to figure out how you would do that. Suppose there are 1,000 studies and 900 of those studies say that chloracne is the only causal disease that is formed by exposure to dioxin that we know of and 100 of those studies, some of the studies that are found in Mr. Daschle's library, indicate otherwise and indicate systemic diseases, soft tissue carcinomas and other things that they believe have a causal relationship to exposure.

How would your panel go about judging and assessing that body of information?

Dr. **Beljan**. The panel would look at the data made available to us, and the scientific methodology, and it would do a critical analysis of how that was done. If the evidence were there to indicate causal or other relationships, then we would certainly recognize it.

Mr. **Edgar**. The mortality study that the Ranch Hand group, through the Air Force, has just released, would you consider that a good study, a mediocre study, a valuable study, in the examination of the literature. Do you think it is statistically——

Dr. **Beljan**. We have not had the opportunity to see the full study. We would welcome the opportunity and would like to do that within the next month.

Mr. **Edgar**. Isn't it true that at the time that you were doing your research and reviewing the literature the Ranch Hand material was not available to you, both the morbidity and mortality study, the twin study was not available to you, the study that's being done by the Centers for Disease Control in Atlanta was not available to you?

Dr. **Beljan**. That's true. The AFIP study was also not available to us.

Mr. **Edgar**. So most of the literature that you were reviewing was literature that was dated pre-1981, is that not correct?

Dr. **Beljan**. That's correct. At the time of this report.

The resolution, however, asked our committee, in light of the information that is now being made available to us, to do a critical analysis of that information to review it and to update this update, which is what we intend to do.

Mr. **Edgar**. So your paper surge as of 1981 didn't come up with any conclusion?

Dr. **Beljan**. Our extensive publications review and critical analysis did not come up.

Mr. **Edgar**. Suppose that a very well-done study did conclude causality, you're prepared

Dr. **Beljan**. We would be prepared to embrace that if the study, in fact, showed that and the rigor of the study supported the conclusion, from a scientific basis.

Mr. **Edgar**. I am really pleased to have you before our committee today because you are the experts and from your expert opinion based on your review of the literature why did the Federal Government expend $30 million to remove families from that particular community because of exposure?

Dr. **Beljan**. I would like to say that you pay me the compliment of giving me a scientific expertise and I would answer that question on a scientific basis only. I do not have the facts available to me that would permit me to make the judgment of why the actions were taken at Times Beach and elsewhere. I would not like to make a comment on that because that would be conjectural.

Mr. **Edgar**. Don't you think that is startling based on your review of literature? Isn't it startling that any agency of the Federal Government would take that kind of emergency action to remove families from exposure to dioxin? I mean, it is unheard of to go out and buy up people's family homes because of higher incidences of illness.

Dr. **Beljan**. Mr. Edgar, as I get older, sir, I am not startled by anything.

Mr. **Edgar**. I guess the point that I am making is that in a lot of areas, we have one in New Jersey now where agent orange was produced, we have the Love Canal problem, we have exposure to other chemicals and we are becoming much more sensitive. As Congressman Daschle pointed out, tobacco was not considered very dangerous to anyone until we began to understand its implications to the body and I would wonder whether or not there isn't a growing body of evidence that this chemical which you determine as one of the most toxic chemicals known to man, would do more than just simply cause chloracne in certain people.

I was amused with your story about the guinea pigs have a higher incidence than other forms of the same species. I would wonder whether enlisted people might, as guinea pigs, have a higher incidence of systemic diseases than officers and whether or not, if we do determine causality, we'll find that in specialties of people.

But it seems to me that we are becoming a chemical conscience nation. We're discovering the implications of our civilization on our bodies and our lives and the action in Love and Times Beach demonstrates that chemists and scientists examining the parts per million of dioxin in the soil and in the ground and the systemic diseases that families are being exposed to are becoming much more increasingly alarmed about the problem. My guess is that a GI in a foxhole exposed to some of those very same chemicals, whether it's agent orange, purple, green, or whether it is some kind of chemical used in their weapons, might also have systemic diseases related to that.

Congressman Daschle raises a goood point. By the time everybody's literature is published and every "i"is dotted and every "t" is crossed, some deaths will occur and some long-term systemic illnesses will occur without compensation.

Dr. **BELJAN**. I would like to respond to that because I think your points are well taken. There are many, many factors that entered the decision regarding Times Beach and elsewhere. Some of them obviously reflect the concern of the communities involved of which you speak and in which some of the action may be predicated on factors other than blunt, cold, scientific fact. I recognize that.

However, I think it is important to point out that if our expert panel saw the strongly suggested evidence that you are intimating in the statements which you have made, then I am sure our report would have a very different flavor. We did not find that kind of evidence in the literature available to us that we subjected to critical, scientific analysis.

In regard to the questions of lethal toxicity, I have already alluded to the problem of making direct extrapolations of animals to man, as well as the problems within various animal species themselves regarding these agents. But one has to look at age differences, one has to look at the compounds themselves. As you know, there are 22 isomers of TCDD, there are over 80 potential compounds in that family. Some of the studies that we have talked about showed mixtures of these, so even some of the animal data has to become suspect. The method of ingress of the agent, its bioavailability, its absorption—these are important questions that we can't answer in the press or in congressional hearings. We have to do this by a careful review of the scientific facts made available to us.

So our posture, although it seems to be very cold, is one which is based on the facts that we have been able to glean from an intensive review of the world literature available to us. Our committee will, in its next several meetings, do an extensive review of what has happened and transpired in the past two years since our last report. It will not be from newspaper accounts. It will not be from television coverage. It will be from the review of the scientific literature dealing with this specific problem.

Mr. **EDGAR**. Thank you. I have no further questions.

Mr. **APPLEGATE**. Thank you, Mr. Edgar.

Chairman **MONTGOMERY**. Thank you, Mr. Chairman. I would like to thank Dr. Beljan and the other members of the panel for being here today. The American Medical Association is certainly well respected on the Hill and, as far as I am concerned, it is one of our fine leaders in medical care. I want to thank you for coming up here and telling us the rather tough stand you have taken and I want to commend you for it.

The problem I have is that, as chairman of the full committee we are only going to get so much money to take care of the veteran. For medical care, compensation, and pensions, we are only going to get a certain amount of the slice of the pie. So we have to put priorities on these matters as to which is the most important and what we are really trying to determine is how much effect agent orange has had on the Vietnam veteran. As I said earlier today and I will repeat it again, I am seeing more and more of a problem of the Vietnam veteran in the psychological area and jobs—it's unbelievable. The Vietnam era veteran—a nonveteran can get a job over the Vietnam era veteran and these are problems that worry me.

Only one comment or question. My great grandfather was a researcher way down in the South and our family is not very proud of it, but he brought Johnson grass to the South and those people from the Deep South know that Johnson grass is not very likable and doesn't really do a good job and we have been trying to defoliate and get rid of Johnson grass for the last 85 years.

Are the defoliants that we use and the herbicides that we have used in the Southland, how does that compare with agent orange? Is it the same thing or what's the difference?

Dr. BELJAN. I would like to not respond in general to that question, sir, but to my knowledge, I do not know of any adverse effects at this time.

Mr. MONTGOMERY. I am just trying to compare the——

Dr. BELJAN. I will plead ignorance on this point. If I knew the names of the compounds and so forth, I think I might be able to respond a little more accurately.

Mr. EDGAR. It seems to create a conservative attitude among those who eat the food in that neighborhood. [Laughter.]

Mr. MONTGOMERY. Well, you know, it's rubbing off on Mr. Edgar, too. I have seen a lot of conservatism in the last 4 or 5 years in Mr. Edgar and the others. [Laughter.]

Mr. EDGAR. Mississippi catfish, I think.

Mr. MONTGOMERY. Yes.

I am really just asking. I know that I guess Mirex is more geared toward the animal life than it would be, but I know in the Delta they use a number of chemicals to clean out cotton, but there's been no comparison in your panel of those chemicals that have been used to defolitate in farming?

Dr. BELJAN. Our emphasis in the study that we reported was largely related to 2,4-D and 2,4,5-T. We did not go into the total gamut of other herbicides.

Mr. MONTGOMERY. I thought someone mentioned that these chemicals were used in agriculture.

Dr. BELJAN. Absolutely, and 2,4-D, particularly, has been used in Oregon and California for 35 years with very little report or allegations of toxicity.

Mr. MONTGOMERY. Well, these same chemicals, agent orange, are used in agriculture.

Dr. BELJAN. That is correct and, as you entered properly in the record this morning, even 2,4,5-T—which is the problem because it is contaminated in its manufacture by dioxin, has not been totally restricted in the United States from use and it is not totally restricted in the United Kingdom and other countries.

Mr. MONTGOMERY. Thank you, Mr. Chairman.

Dr. **Beljan**. Mr. Chairman, may I please indicate that we do want to be helpful and we regard the problem that your body faces with gravity. We hope that we will be able to undertake a detailed review such that, if the facts warrant, will most certainly change our report. We would hope to make our report available to you. We will give our honest, objective review of information available to us, if it is available in the world's open literature.

Mr. **Edgar**. Would the chairman yield?

Mr. **Applegate**. We really appreciate that, Dr. Beljan. Yes, Mr. Edgar.

Mr. **Edgar**. Would the chairman yield just for one comment?

I wonder if you might in your review also look at the concentration of the use because I think the chairman asks a good question about its use in other States and in other forms of agriculture. I was struck by the comment by the person from the Air Force talking about it used full strength in the planes in Vietnam and I wonder if that same full strength is used on a normal basis in agricultural consumption.

Dr. **Beljan**. It's usually not.

Mr. **Applegate**. Yes, that would prove very valuable to us.

I, also wish to reiterate what our chairman has stated, that we thank you very much for your testimony, your expertise and that of the American Medical Association, not only to this committee, but to the many committees throughout the Congress.

One request. If you would, send us a copy of the resolution so that it may be included in the hearing record.

Dr. **Beljan**. We can leave it with your clerk, sir, and would be pleased to do that.

[The information follows:]

RESOLUTION ADOPTED BY THE AMERICAN MEDICAL ASSOCIATION IN JUNE 1983

Resolved, That the American Medical Association institute an active public information campaign to get accurate information on dioxin before the public to prevent irrational reaction and unjustified public fright and to prevent dissemination of possible erroneous information: and be it further

Resolved, That the AMA Council on Scientific Affairs be requested to update its 1981 report on dioxin.

Mr. **Applegate**. There may be some questions that will be submitted by various Members at a later date. If so, we would appreciate your answering them if we transmit them to you.

Dr. **Beljan**. We would be delighted to be helpful in any way possible.

Mr. **Applegate**. Thank you very much for appearing before us here today.

Next we have Dr. Franz M. Enzinger, Department of Soft Tissue Pathology, the Armed Forces Institute of Pathology.

Doctor, you have a statement and if you would, in the interest of brevity, please summarize your remarks. Your complete statement will be made a part of the record. We appreciate your being with us here this morning.

STATEMENT OF DR. FRANZ M. ENZINGER, DEPARTMENT OF SOFT TISSUE PATHOLOGY, ARMED FORCES INSTITUTE OF PATHOLOGY

Dr. **Enzinger**. Mr. Chairman and members of the committee, my name is Franz M. Enzinger, M.D. I am a pathologist and Chairman of the Department of Soft Tissue Pathology at the Armed Forces Institute of Pathology in Washington. I have prepared a written statement on the current distribution and clinical behavior of soft tissue sarcomas and on the case control study that we are conducting jointly with the Veterans' Administration.

I will be pleased to answer any questions you or the Members of the committee may have.

[The prepared statement of Dr. Enzinger appears on p. 167.]

Mr. **Applegate**. Thank you very much. That was a very brief summary.

Dr. **Enzinger**. Did you want me to read my prepared statement?

Mr. **Applegate**. No, we will go ahead. We do have some questions which members of the committee would like to pose at this time.

Chairman **Montgomery**. Thank you, Doctor. I wish a number of witnesses could learn to summarize as quickly as you have done. [Laughter.]

We would move much faster here on the Hill. I will go back to a question I asked earlier about the soft tissue and about the liver. That's part of this bill—the latency of showing up, the time factor of being exposed to dioxin. Would you give your feelings in this area?

Dr. **Enzinger**. We have really no exact data, I think, on the latency period or a time factor following agent orange exposure but judging from other studies let's say, radiation induced development of soft tissue sarcomas we know that it takes at least 2 years to develop such a tumor and probably between 2 and 15 years in most of the cases.

So the time factor between exposure and development of the tumor ranges somewhere between 2 and 15 years and perhaps in rare cases it may be more than 15 years.

Mr. **Montgomery**. Well, I think Mr. Daschle will agree with me. If we can get some time factors in, it might—you said between 2 and 15 years.

Dr. **Enzinger**. I cannot give any more precise estimate. I think it varies from case to case and I cannot give any more accurate latency period for any specific cause.

Mr. **Montgomery**. Thank you.

Mr. **Applegate**. Thank you, Mr. Montgomery.

Mr. **Daschle**. Thank you, Mr. Chairman. I will be very brief.

Related to the question posed by our chairman, NIOSH, which I know everyone is familiar with, the National Institute for Occupational Safety and Health—in their study they found one Monsanto worker, who in 1978 at the age of 58 died from a malignant fibrous histoma some 29 years after an accidental exposure spill of PCP. It also resulted in chloracne. So 29 years afterwards, in some cases, you can establish that relationship. You are familiar with the NIOSH dioxin worker registry, are you not?

Dr. **Enzinger**. Yes, I am.

Mr. **Daschle**. From what I understand, in your testimony you didn't incorporate any of their report or any of their statistics nor did you incorporate the National Cancer Institute figures which showed a 771-percent increase from the 1950's to the 1970's in soft tissue cancers among women in Midland, Mich. They seem to be studies that other scientists have presented to the committee as evidence of some relationship. Why did you choose not to incorporate those into your work?

Dr. **Enzinger**. Well, at the time I wrote my statement I was not aware of the last Monsanto study reported by Zack and Gaffee. They reported they studied 884 men who worked at the nitro plant in West Virginia. Of those 163 had died, compared to 158 expected to; 35 of those had malignancies, but there was only one soft tissue tumor among the 35 malignant neoplasms.

Mr. **Daschle**. So you were not aware of some of this information when you wrote your testimony and the report, is that correct?

Dr. **Enzinger**. I was not aware of all of the information. That's correct, sir.

Mr. **Daschle**. I just didn't know because obviously those are pretty significant statistics here and any complete analysis would want to include those as well, I would think. I appreciate, too, your brevity this morning.

Thank you, Dr. Enzinger.

Mr. **Applegate**. Doctor, thank you very much for appearing before the committee.

You have stated that you have examined and diagnosed approximately 30,000 soft tissue sarcomas that were submitted for consultation to the Armed Forces Institute of Pathology. What are the primary causes of these sarcomas?

Dr. **Enzinger**. We know very little about the causes of soft tissue sarcomas. We know that some soft tissue sarcomas develop secondary to ionizing radiation damage. We know that others occur following chloride exposure and that still others are secondary to asbestosis. But in most soft tissue sarcomas we do not know the cause.

Mr. **Applegate**. Thank you very much, Doctor. We sincerly appreciate your appearance before the committee and your testimony. We'll be reading and digesting it and it should prove valuable to us. Thank you.

The next witness we have is Dr. Michael Luster from the National Institute of Environmental Health Sciences. Dr. Luster.

I would like to reiterate to all of today's witnesses that we, as individual members of the committee, may have questions that we may wish to submit and we would ask that all witnesses be available to answer them through the mail.

Dr. Luster, thank you very much for being with us. You may proceed. You may summarize your statement, if you wish.

STATEMENT OF DR. MICHAEL LUSTER, SCIENTIST, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, NATIONAL INSTITUTES OF HEALTH

Dr. **Luster**. Mr. Chairman and members of the subcommittee. I am a scientist with the National Institute of Environmental Health Sciences, a component of the National Institutes of Health. My field of research interest is immunology.

For the past 7 years I have conducted research investigating the immunological changes that occur following exposure to various chemicals of environmental concern, including dioxin in rodents. I have published a number of scientific papers on the subject. I am here today at your request to discuss the immunological effects of dioxin on laboratory animals.

As was communicated to the subcommittee staff, I have no expertise with regard to the details of H.R. 1961, and therefore, I am not prepared to discuss it. What follows is a brief summary about what is known about the effects of dioxin on the immune system of laboratory animals. Following my formal written remarks, I ask that the committee include a more detailed review article as part of the hearing record.

Dr. **Luster**. Animal studies have clearly demonstrated that dioxin may alter components of the immune system in a number of laboratory animal species. Animals exposed early in life, either prenatally or postnatally appear more immunologically compromised than animals as adults in that a variety of immune responses appear altered. In contrast, animals exposed during adult life demonstrate only depression of antibody synthesis. There is some evidence in laboratory animals that low doses of dioxin stimulate immune responses while higher doses produce immunosuppression, a phenomenon also seen with other chemicals.

It has been reported that studies of immune function in Seveso children with chloracne revealed either no effect or a mild stimulation. If these data are correct—details of the data remain unpublished—and they need independent review, one may speculate that chloracne is an earlier sign of acute dioxin toxicity than is immune depression. Draft reports of immunological studies of English workers industrially exposed to dioxin remain unpublished, unconfirmed, and report incomplete data. Thus, interpretation of the reported findings is not possible.

Thank you. That concludes my testimony.

[The prepared statement of Dr. Luster appears on p. 172.]

Mr. **Applegate**. Thank you.

Mr. Daschle.

Mr. **Daschle**. Dr. Luster, the testimony that we have received before in the Congress indicated that there is some evidence in Dow research which says that at certain threshold levels, there occurs an immunological breakdown. From what you said, you seem to confirm that, is that correct?

Dr. **Luster**. Laboratory animals clearly confirm that dioxin causes immunosuppression in animals.

Mr. **Daschle**. In laboratory animals. So that is, I think, a very important factor here in all of this. We have tried to decide just what it is that brings us this relationship between exposure and some of these diseases and others in the scientific community that it could be this immunological breakdown that we find in laboratory animals that show that.

Dr. Prince studied the immunological breakdown of the railroad workers in Illinois and came to the same conclusion. Even though your statement today was brief, it was very important. I am grateful to you for it.

Thank you.

Mr. **Applegate**. Thank you, Mr. Daschle, and Dr. Luster, thank you very much for appearing before the committee. We appreciate your testimony and the article which you have submitted as well. It will be very useful in own work ahead.

We next have Dr. Karl Anderson of Rockefeller University Hospital. Dr. Anderson, welcome to the subcommittee. You may proceed as you wish. We are under the 5-minute rule and we would appreciate it if you could summarize your remarks.

STATEMENT OF DR. KARL ANDERSON, ROCKEFELLER UNIVERSITY HOSPITAL

Dr. **Anderson**. It's a pleasure to be here today to briefly summarize current knowledge about porphyria cutanea tarda [PCT] and how the disease may relate to genetic factors and environmental chemicals such as dioxin. I have prepared a written statement which I will summarize.

The porphyrias are a group of disorders which are due to specific metabolic defects in the body. PCT is the most common of the porphyrias. Both acquired and genetic forms of PCT occur in the general population. In addition there have been a few outbreaks reported from TCDD (dioxin) exposure. PCT can be associated with skin changes and mild or moderate liver damage. Neurological effects can occur in certain other types of porphyria but do not develop as a result of PCT.

A deficiency of the same enzyme is found in both acquired and genetic forms of PCT and additional factors such as iron, alcohol, and estrogens can contribute to both types of PCT. The prevalence of PCT has not been accurately estimated in most localities. It does appear to be more common in countries in which alcohol consumption is high. It is generally more common in men. More recently the relative frequency of female patients has been increasing due, in part, to oral contraceptive use, postmenopausal estrogen treatment and alcohol consumption. It also rarely occurs in children.

PCT occurs in relation to liver disease, as I have already mentioned. It also occurs in association with diabetes mellitus, certain immunological disorders, including lupus erythrematosus and, in some patients on hemodialysis machines, more frequently than would be expected by chance.

The chief symptom of PCT is photosensitivity of the skin. This occurs on sun-exposed areas and is manifested by blisters which can be large and painful and by increased fragility of the skin. Scarring and secondary infection can result. The specific metabolic defect associated with PCT is a partial deficiency in the liver of an enzyme termed "uroporphyrinogen decarboxylase" or "URO-D". This is one of eight enzymes which comprise a metabolic pathway to make heme in the body from simpler molecules. Several porphyrins are intermediates in the later portion of the synthetic pathway for heme. URO-D carries out a complex transformation of one of the porphyrins, namely uroporphyrinogen, in the pathway.

When URO-D is deficient, as in PCT, body tissues can still make enough heme, but because of the partial deficiency of URO-D this occurs at the expense of excess formation of porphyrins and excess porphyrin accumulation in the body.

In PCT, porphyrins gradually built up in the liver and then spill over into the blood plasma which carries them to the skin. Because porphyrins first accumulate in the liver in PCT and because there is regularly some degree of liver damage, the disease is classified as one of the hepatic porphyrias. The blood plasma also carries excess porphyrins to the kidneys and porphyrins are then excreted in urine. Some of the excess porphyrins are also excreted in bile by the liver and these appear in the feces. This results in a characteristic pattern of porphyrin excretion in urine and feces in this disease.

Research findings published approximately in the last 10 years have added considerably to our knowledge of PCT. It has become clear that in a substantial minority of patients a genetic deficiency of URO-D underlies the disease. However, most patients with PCT appear to have a truly sporadic or acquired form of the disease. In these individuals, URO-D is deficient only in the liver, whereas in the genetic form, it is deficient in all tissues. Why the liver enzyme becomes deficient in patients with the sporadic disease is not known.

Thus, there are at least two forms of PCT, both occurring rather uncommonly in the general population. The clinical manifestations and porphyrin patterns in the genetic and the acquired forms are little, if at all, different. It is possible to distinguish the genetic form of PCT by finding low URO-D in tissues other than the liver, as for example, in red blood cells. Assays for URO-D are difficult and therefore not widely available at the present time.

Research in laboratory animals has also provided important new knowledge, particularly about the relationship of PCT to chemical exposures. It is known, for example, that chlorinated hydrocarbons, including dioxin, can inhibit URO-D in animals and produce a condition closely resembling PCT.

This first became of interest in the late 1950's when there was an epidemic in eastern Turkey of a PCT-like syndrome in humans. This resulted from seed wheat which was contaminated with hexachlorobenzene, a fungicide, and this was mistakenly used for food by a large, impoverished population. It was estimated that over 3,000 persons developed porphyria with intense skin symptoms as a result of this toxic chemical exposure.

There have been smaller outbreaks from exposure to other cyclic chlorinated hydrocarbons, including dioxin. One was in 1964 in a Newark plant where 2,4-D and 2,4,5-T were manufactured and in that case 11 workers were found to have increased uroporphyrins and two had skin manifestations consistent with PCT. Also there was an outbreak in Czechoslavakia between 1965 and 1968 also in a plant for the manufacture of 2,4,5-T.

In subjects exposed to TCDD porphyrin flourescence in the liver is quite prevalent, even with little or no increase in urine porphyrins. Improved industrial hygiene in these plants substantially reduced the prevalence of PCT and excess urinary uroporphyrin among the workers. The possibility is worth considering that inapparent exposure to such industrial and environmental chemicals may predispose to the development of some of the sporadic cases of PCT that we see in the general population.

That concludes my summary. I would be happy to answer any questions.

[The prepared statement of Dr. Anderson appears on p. 200.]

Mr. APPLEGATE. Thank you very much, Dr. Anderson.

In your estimation, how long after exposure to dioxin do the first signs of PCT manifest themselves?

Dr. ANDERSON. Well, in the two industrial outbreaks in Newark and in Czechoslavakia, which have been described in some detail, PCT occurred during the industrial exposure and the cases improved fairly rapidly after the exposure was terminated or the conditions in the plant were improved. So I would say it was probably a matter of months. Some of the workers had worked in those plants for a number of years and some of them had worked there for just a few months so it's difficult to know.

Mr. APPLEGATE. So it could be within a matter of months?

Dr. ANDERSON. Right.

Mr. APPLEGATE. It's usually not immediate though.

Dr. ANDERSON. Right. There was no mention in those articles of a suspicion by the physicians who wrote the articles that there was a long latency period. Their emphasis was on cleaning up the exposure and when they did that they found that there was a sharp decrease in the incidence of the disease.

Mr. APPLEGATE. Could this latency period extend for a number of years after exposure?

Dr. ANDERSON. Well, the people who were examined were working in the plants at the time. Some of them had worked there for a few months, some of them had worked there for several years. These were workers who were chronically exposed to very high levels of dioxin, although there was no way to quantitate how much dioxin was actually in their bodies. They were exposed, externally at least, to large amounts of dioxin for long periods of time. Some emphasis has been placed on the fact that chronic, high exposures are an important factor in dioxin-related disease, including PCT.

Mr. APPLEGATE. Mr. Daschle.

Mr. DASCHLE. No questions, Mr. Chairman.

Mr. APPLEGATE. Does counsel have any questions?

Mr. MOON. One question, Doctor. If a person was exposed for a relatively brief period of time, say, 1 year, and then that exposure terminated, how much time would elapse before you would expect the symptoms to appear and what would you consider the outside time limits for it to be attributed to that exposure?

Dr. ANDERSON. I would expect, based on the few reports in the literature, that if he was going to develop PCT due to that exposure that it would occur during that 1-year period or perhaps within a few months afterward. I know of no reports of cases of PCT developing years after exposure.

Mr. **Daschle**. Will the chairman yield?

Mr. **Applegate**. Yes.

Mr. **Daschle**. I would call to the attention of the committee the testimony of Dr. Hyman Zimmerman who was asked that same question and he said that there is no certainty with which we can attribute a certain time limit. Dr. Zimmerman says that it may be quite a period of time and that it's very difficult to lock that time description of that kind. Would you not agree with that?

Dr. **Anderson**. I would agree with that. I would only say that from reviewing the literature there have been no reports of a long latency period.

Mr. **Daschle**. That's right. There is no literature to that extent, but certainly that doesn't preclude future scientific evidence from conflicting with what literature there currently exists.

Dr. **Anderson**. Well, in the future. But currently there is no evidence.

Mr. **Daschle**. That's right. Thank you.

Mr. **Applegate**. Thank you very much for your testimony. We may have some questions that we will submit to you.

Next we have Dr. John Bederka with the University of Illinois Medical Center. Dr. Bederka is with the department of pathology. We welcome you to the subcommittee, Doctor.

STATEMENT OF DR. JOHN BEDERKA, DEPARTMENT OF PATHOLOGY, UNIVERSITY OF ILLINOIS MEDICAL CENTER

Dr. **Bederka**. Thank you very much. It's a pleasure to be here. I have submitted a statement which I am sure you will all read at the time you find appropriate. I do have some transparencies which summarize what's in the prepared speech and these transparencies I would like to project on the screen because they will allow me to emphasize the few points that I briefly want to make.

Mr. **Applegate**. I think if you pull the microphone over to this side, it would be helpful to you, and if anyone wants to move over to this side of the room and take a seat down around here, you will be able to see here.

Can you flick a light over there to darken that side?

Thank you, Vance.

Dr. **Bederka**. After 20 years of lecturing, I can't turn on the overhead projector.

Mr. **Applegate**. That's all right. I can't drive a nail either.

Dr. **Bederka**. Well, success. Thank you, sir.

I may just have to make the points verbally. What I have here is briefly I want to introduce this thing with the fact that I want to make three major points in the presentation regarding the human. I would like to show you and try to convince you and present information that there are three major systems that are affected in the human due to dioxin-related exposures.

One is a severe and quantifiable immune disfunction. The other is chloracne and the third is probably certain types of cancers, as have been alluded to earlier today.

The animal data clearly show that many systems are affected in toxicologic terms, but, more specifically, in terms of cancer. We all start off probably as one cell which is indicated down here more or less after it is divided and it continues to divide and grow into an embryo. The embryo then branches off and produces all of our systems. There are three major portions of the embryo—the ectoderm, mesoderm and the endoderm. Tissues from all parts of the endoderm are affected by dioxin and dioxin-type chemicals, but specifically TCDD. The brain, the skin, the blood, the liver, the thymus. There is no tissue in the body, basically, that isn't affected by dioxin in the animal.

In the human I have specifically pointed out a few here. Thymus-related activities, which is the immune system, are affected. Muscle, apparently soft tissue sarcomas; the blood system and lymph cells, the epidermis and, again, the central nervous system. These are all, again, from all parts of the embryo, indicating that dioxin can apparently affect all systems and has very little selectivity.

What I would like to do is focus on the immune system because that's where the quantitation is best and that's where we will probably see the most abilities to really get at this point.

Dr. Prince, Joe Prince—he has still not finished up his work—has been working with me and the committee to produce some of this stuff based on humans that were exposed to chemical cleanup down in Missouri and the details of that could be made available, if you so request. But what he has looked at is the immune system of these people and tried to see whether the immune function was compromised.

The point to make here is that the blood cells start from the bone marrow. Some of them go into the thymus and other parts of the body and they became capable of regulating the normal function of the whole body.

They regulate the immune system. The immune system keeps us going in terms of viral infections, bacterial infections, lets cells know who is here and who isn't here, in other words, recognition. Cells talk to each other chemically. The immune system takes care of all this.

Going directly to the results of the immune system that Joe has found in the workers, and I have also added here Dr. Ward's results that we briefly have had a chance to look at and so label Dr. Ward's with a "W."

There are 10 points that I think can be made at this time. The white blood cell levels were significantly increased. I use significantly meaning statistical at the P -.05 value or lower. The eosinophil count was also elevated significantly. This can be measured by almost any good laboratory.

Dr. Ward has shown in his group that the IgM levels were significantly decreased—these are antibodies, immunoglobulins, that work against viruses and bacteria and so forth. He also showed in some parts of his exposed populations that the IgD levels were also decreased and this is involved in the immunologically-competent communication. If they don't communicate, the immune system, and it doesn't fight off bacteria, viruses, probably extracellular growths an other things.

Joe Prince has studied binding and he has found that the bacterial binding in the cells from these exposed people were not as competent as they should have been and this was significantly different. He looked at bacterial binding with B-cells and he looked at bacterial binding with the T-2 subset, which is supposed to get involved with making the B-cells work and their functions were both decreased indicating that the system just isn't working.

The Mitogen stimulation tests were also done and the PHA stimulation that was done by Dr. Ward and Joe did that also. They basically agreed that the Pokeweek Mitogen stimulation was increased, which shows that the B-cells are not being controlled actively. The T-cells were looked at phytohemaglutinin and they were decreased, which shows that they are not doing their job actively on the B-cells. So it sort of ties together.

A new test was developed along with the Packard Co., by Joe Prince to do chemiluminescence work to look at functions of neutrophils. In addition to just engulfing do they actually do something after they take in the bacteria or other things and destroy them. And in some parts of the population, these functions are also significantly reduced—the neutrophil levels of ATP, the energy bundles were also decreased.

If you look overall at the whole white blood cell picture shows a significantly decreased capability at the P —.003 level which is at 3 parts per thousand. It's a very significant alteration to any immune function. This is all pretty well quantifiable.

The chloracne thing I will just summarize briefly. Chloracne—it's a fuzzy picture; that's why it's a fuzzy slide. But 5 percent or more of any population exposed show chloracne at some time or another, within days or years it can come about.

My conclusion is that this chloracne is not just a skin disease or a skin rash, but a type of neoplastic growth. The cells, if you look at them, are dedifferentiated epidermal cells and show some lack of control. My basic appreciation for how dioxin works is that it is a exogenous hormone that displaces the steroids normally used to regulate cell growth and we will address this topic at a later time.

The point about chloracne is that if you see it, it's obviously there. It doesn't necessarily indicate other systemic disease. However, it isn't there, this does not preclude the existence of systemic disease. It's a very good indicator but it's probably dose-related and, in most cases where chloracne has been studied, the dose of the exposed population was not known. So it's difficult to get too excited about that, but it's one other indicator that the human is in trouble.

I would like to summarize at this point, also addressing the idea of the soft tissue sarcoma cancer idea, Dr. Hardell and the group and other people have looked at this and their conclusions are that the phenoxyacid herbicides that are contaminated affect these people, mostly skin related. Many of them have chloracne in addtion to or prior to the soft tissue sarcomas that have been described—Hodgkins and Hodgkins-types of lymphomas. Onsets are in the literature to be looked at.

They also made a very important point in that they seem to have been able to calculate multiple exposure effects in their populations and these types of multiple exposure effects very closely seem to resemble the Vietnam veteran multiple exposure circumstance, and that needs to be looked at very cautiously. That was pointed out in much of the testimony today.

So, in summary then, that the immune dysfunction of the system, probably in the human and in all of the animals is the real basic problem in the organisms finally succombing to disease. This regulates the system; it can be hyperfunctional and hypofunctional and that's why I use the word "dysfunction." If the immune system isn't working, this signifies that cell-cell communication is out of whack. This would lead to increased susceptibility to disease and increased susceptibility to abnormal cell growth. Both the chloracne and the cancers and other types of things fall into this category, and that seems to be pretty much where the status of our information base is right now.

Thank you very much. I would be delighted to try to answer any questions or think about some questions with you.

[The prepared statement of Dr. Bederka appears on p. 206.]

Mr. APPLEGATE. Thank you, Dr. Bederka.

I don't have any questions at this point. I believe that we will have some that we will be submitting to you and ask that you answer them for us. But at this time I would recognize Mr. Daschle.

Mr. DASCHLE. Thank you, Mr. Chairman.

I just wish that Dr. Bederka's testimony would ~~have~~ been earlier in the day and I know for obvious reasons it couldn't be. But, it's really a profound bit of assistance to us. It puts some reason, some understanding, a better perspective, at least for me, and I'm very grateful to Dr. Bederka for that. It really makes me wonder, though, how on the basis of the information that you have, obviously with the tremendous evidence that exists for what you've just presented, that there are organizations which say there is just no evidence, there's just nothing there that gives them cause for concern.

On the basis of what you've presented, on the NIOSH study, on the National Cancer Institute figures, I can't imagine that we can just turn our heads and look the other way with that kind of an overwhelming amount of evidence. So, you really have done the committee a service and I hope to work with you in the future as we progress.

Thank you, Dr. Bederka.

Mr. APPLEGATE. Thank you, Mr. Daschle.

I must agree that it is often confusing to those of us who command such little knowledge in this field when we receive two opposing points of view and are then asked to arrive at a very difficult decision based on these opposing views.

In any event, we do appreciate your being here today, providing us with some very valuable information which will be necessary for us to conclude what we have set out to do.

Does counsel have any questions?

Mr. MOON. No questions.

Mr. APPLEGATE. Thank you very much, Dr. Bederka. I appreciate your being here.

[Whereupon, at 12:24 p.m., the hearing was concluded.]

APPENDIX

THE TESTIMONY
OF THE HONORABLE LEON E. PANETTA
BEFORE THE
SUBCOMMITTEE ON COMPENSATION, PENSION, AND INSURANCE
OF THE
COMMITTEE ON VETERANS' AFFAIRS

July 12, 1983

Mr. Chairman, as vice chairman of Vietnam-era Veterans in Congress (VVC) and as an original sponsor of H.R. 1961 to establish a presumption of service-connection for certain health problems experienced by Vietnam veterans, I am again honored to have the opportunity to testify before this Subcommittee on the issue of Agent Orange.

As I stated in my testimony of April 26th of this year, I am not in the position to argue the scientific merit of available statistical and medical data relating to dioxin poisoning and herbicide (2,4,5-T) exposure. In this regard, I applaud the Subcommittee for soliciting testimony from the scientific community concerning potential health hazards associated with exposure to highly toxic chemicals. What I wish to address today is the nature and extent of the government's obligations to gravely ill Vietnam veterans who, while in the service of their country, were exposed to extremely toxic chemical agents.

Mr. Chairman, I do not suggest we abandon reason for the sake of compassion. However, at some point a line must be drawn as to how much evidence must be obtained before action can be taken to assist dying and seriously ill Vietnam veterans. I need only to point to the massive cleanup and relocation effort at Times Beach, Missouri following the discovery in that community of the same deadly dioxin known to have been present in Agent Orange, as evidence that other branches of the Federal Government recognize the serious health risks associated with dioxin exposure. Can it be that dioxin found in Agent Orange is any less deadly than that found at Times Beach?

On the basis of testimony recently presented in federal court, we know today that the chemical companies involved in manufacturing Agent Orange were aware of dioxin's extreme toxicity and its presence in Agent Orange at least as early as 1965 when a private meeting was held to discuss the issue. It has also recently come to light that the Joint Chiefs of Staff were advised in 1967 of sharp increases in health complaints among Vietnamese villagers living in areas sprayed with the dioxin-contaminated defoliants. In fact, herbicide spraying continued for almost a year following the release in 1969 of a study sponsored by the National Cancer Institute that linked dioxin exposure to birth defects in laboratory animals. The report was later used by the Department of Defense as the basis for terminating the program.

These are but milestones in a tragedy which today, over a decade later, remains largely unresolved.

Time is running out for hundreds, possibly thousands of Vietnam veterans. Joan Z. Bernstein, chairperson of the original Interagency Work Group on Phenoxy Herbicides, stated over three years ago:

> In short, we may be left, after the research is done, with many of the same social policy issues we face today.

Each step of the path toward resovling this issue has seemed interminable to veterans and their families. At issue is the integrity and credibility of the Veterans Administration's compensation program.

H.R. 1961 is not a reckless response as VA officials would have us believe. The legislation covers three specific disorders, drawn from existing medical literature: soft-tissue sarcomas (cancer), porphyria cutanea tarda, and chloracne. Enactment of H.R. 1961 would restore credibility to the VA's Agent Orange policy and our commitment to compensate veterans for injuries incurred in the service of our country.

Not years, but decades have elapsed since the dangers of dioxin first came to light. We must demonstrate that we are prepared to act by approving H.R. 1961 and shifting the burden of proof from the veteran to the VA in awarding service-connected disability claims for illnesses attributable to Agent Orange.

I thank Chairman Applegate and the members of this Subcommittee for convening today's important hearing and for allowing me the opportunity to participate.

STATEMENT BEFORE THE SUBCOMMITTEE ON COMPENSATION, PENSION AND INSURANCE, HOUSE COMMITTEE ON VETERANS' AFFAIRS

July 12, 1983
by
Congressman William R. Ratchford
5th District, Connecticut

Mr. Chairman, let me start by taking a moment to express my deep appreciation for the opportunity to testify before the Subcommittee in support of H.R. 2017. The experiences of many Vietnam veterans in my district and in the state of Connecticut have disturbed me for many years and I am firmly convinced that the legislation proposed by my colleague Mr. Daschle will go a long way toward righting a very serious wrong.

The Veterans Administration reported this spring that Vietnam veterans have made more than 369,000 visits to VA hospitals for treatment of conditions that could have been caused by their exposure to dioxin, a component of Agent Orange. There are two VA hospitals in Connecticut which perform the Agent Orange physicals. The hospital at Newington has performed 570 of these exams since August of 1980. In West Haven, 708 Agent Orange physicals have been conducted since the inception of the program.

The possibility that many Connecticut veterans were suffering from exposure to Agent Orange during their service in Vietnam became urgent enough in 1982 that the legislature concluded that a state-wide investigation was in order. The legislature passed a bill mandating the Connecticut State Vietnam Herbicide Commission which has been in operation now for six months. The Commission has contracted with a non-profit group -- the Vietnam Veterans Agent Orange Victims -- to compile data over the next five years which can serve as a resource and educational tool in aiding affected veterans. Connecticut is just one of a growing number of states where concern over this issue has grown to the point that a state herbicide commission has been established.

Although the study is still in the initial stages, detailed questionnaires have been sent to 1,566 Vietnam veterans in the state. The medical status on 406 of these men has already been compiled. The figures are alarming. In that small population of 406 veterans and their families, there are a total of 540 serious health problems, problems like cancer, neurological damage, miscarriages, multiple birth defects, tumors, serious skin conditions, and unexplained illnesses. Because of understaffing, the statistics on where and when these men served are still being compiled, but the medical findings compel a very close look.

There are individual horror stories in Connecticut of course, as there are all over the country. One veteran who was a crew member for Operation Ranchhand, responsible for the Agent Orange spraying missions, has had three children with multiple birth defects since his service. One child was born without collarbones and with a cleft palate. Another has a third breast, club foot, and a cleft palate. The third died at birth of multiple heart defects. Another Ranchhand crew member has one healthy child, and one child with missing ears and eyelids, a cleft palate, and club foot.

There is no previous history of birth defects on either side of both these veterans' families.

Most of the health problems that have surfaced in Connecticut, however, have been among the men and the families of men who served as ground troops in Vietnam, living in contaminated areas, drinking the local water and eating the local food. Two of these men have had over 100 non-malignant tumors each removed from their bodies since returning from Vietnam. Another veteran recounts how he developed a severe skin rash while stationed in a contaminated area, and was flown out for medical treatment in Okinawa. He continues to suffer from severe acne for which he receives just 40% disability insurance.

Another veteran, a constituent of mine, was in Vietnam in 1968. Like many soldiers he kept a scrapbook of his experiences, but unlike many others, he also kept a list of the places he went and the dates he was there. A check of this list against the list of the Ranchhand spraying missions indicates that he was in several locations that were sprayed with Agent Orange. My constituent has developed serious liver problems, and growths on the internal walls of his kidneys.

The government is not fulfilling its obligations to its citizens in Connecticut or the rest of the country. Connecticut veterans are relatively lucky. Within the next few months, the state will being to conduct various outreach efforts to help inform veterans that they may be affected and what steps they can take to help themselves and their families. The VA is simply not doing its job in the states. Occasional newsletters are not filling the void, and the fact that treatment is at long last available for conditions that may be the result of exposure to herbicides in Vietnam is welcome but ironic. Veterans are asking themselves: if presumptive treatment, why not presumptive compensation? And if the citizens of Times Beach, exposed to dioxin at 120th the level in Agent Orange, why not the citizens who served in Vietnam? When I am asked these kinds of questions, I am embarrassed that I cannot provide a better answer on behalf of our government. I am here to testify on behalf of Connecticut men, women and children who continue to suffer long after the war is over. Let the studies continue by all means. But let's not quibble over the smaller details. Dioxin is a killer and a crippler. VA Administrator Walters has said that he opposes H.R. 2017 in part because it has the "... potential for alarming millions of veterans and the population as a whole." Give us credit, Administrator. We are alarmed. But not only at the spectre of dioxin. At the spectre of indifferent government which inflicts enormous suffering and is too callous to assume responsibility. I strongly urge the Subcommittee's support for this legislation.

Thank you.

MAY 23 1983

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 20 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Honorable G.V. (Sonny) Montgomery
Chairman
Committee on Veterans' Affairs
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

Thank you for your letter of April 27, 1983, concerning the current uses of the herbicide 2,4,5-T.

In March 1979, EPA suspended the forest, rights-of-way and pasture uses of the phenoxy herbicides 2,4,5-T and silvex. The Agency began its risk/benefit evaluation of 2,4,5-T in 1978 due to evidence from laboratory studies indicating that the chemical posed risks of tumor formation, birth defects and other adverse reproductive effects. Use on non-cropland, industrial sites, rangeland and rice are not affected by the current suspension, since these uses involve lower risks of human exposure. At the time of the suspension action, the Agency estimated the annual usage of 2,4,5-T on rangeland at approximately two million pounds, and on rice at approximately 300,000 pounds.

In March 1980, the Agency began hearings to examine the risks and benefits of both the suspended and non-suspended uses of these herbicides. After one year of testimony on risk issues, and just as the presentation of benefits evidence was begun, Dow Chemical and EPA filed a joint motion to postpone further hearings to permit the two parties to consult with other affected parties and devote their full attention to settlement discussions. The suspended uses continue to be prohibited during the period of hearings or negotiation. As we proceed with the settlement negotiations or the full hearings, please be assured that EPA will make every effort to ensure that the risks and the benefits associated with 2,4,5-T are carefully considered.

I hope the information provided is helpful. If I may be of further service, please let me know.

Sincerely yours,

Don R. Clay
Acting Assistant Administrator
for Pesticides
and Toxic Substances

DEPARTMENT OF THE AIR FORCE

PRESENTATION TO THE HOUSE COMMITTEE ON VETERANS' AFFAIRS
SUBCOMMITTEE ON COMPENSATION, PENSION AND INSURANCE

JULY 12, 1983

SUBJECT: Ranch Hand Mortality Study

STATEMENT OF: Major General Murphy A. Chesney
Deputy Surgeon General
United States Air Force

Not for Publication Until Released by the House Committee on Veterans' Affairs, Subcommittee on Compensation, Pension and Insurance, House of Representatives

MAJOR GENERAL (DR.) MURPHY A. CHESNEY

Major General (Dr.) Murphy A. Chesney is Deputy Surgeon General, Headquarters U.S. Air Force, Washington, D.C.

General Chesney was born November 29, 1927, in Knoxville, Tennessee, and graduated from Central High School near Knoxville in May 1945. He attended the University of Tennessee in Knoxville from September 1945 to March 1947 in an accelerated premedical program and graduated with a bachelor of science degree. He earned his doctor of medicine degree in June 1950 from the University of Tennessee's College of Medicine in Memphis.

In June 1951 he completed his internship at the Scott and White Hospital, Temple, Texas, and entered private practice as a surgeon and general practitioner at the Edgar Renegar Clinic in Levelland, Texas. A year later he moved to Rule, Texas, where he was associated with Dr. Robert E. Colbert in the Rule Clinic. While residing there he was elected president of the Chamber of Commerce.

General Chesney entered the U.S. Air Force in April 1955, attended the basic orientation course at Gunter Air Force Base, Alabama, and later the primary course in aviation medicine at Randolph Air Force Base, Texas. In July 1955 he was assigned to the dispensary at Portland International Airport, first as flight surgeon and then as commander. He continued to serve as commander when the dispensary became a hospital.

From July 1957 to June 1960, General Chesney was at the University of Tennessee in Memphis where he completed his Air Force-sponsored residency in internal medicine. During his last year of residency he was appointed chief resident and was involved in several research papers and projects. He also served as a university instructor from July 1959 to June 1960. For the next two years he was assigned as chief of hospital services and chief of the Department of Internal Medicine at Homestead Air Force Base, Florida.

In May 1962 he transferred to the dispensary at Ben Guerir Air Base, Morocco, as commander. He moved to the 401st Tactical Hospital, Torrejon Air Base, Spain, in June 1963 and became deputy commander and senior internist.

General Chesney returned to the United States in June 1966 and assumed command of the 852nd Medical Group at Castle Air Force Base, California. He became director of professional services in the Office of the Command Surgeon Pacific Air Forces, in August 1969 and deputy command surgeon in June 1972. While there his duties included supervision of the professional medical care of patients, including combat-injured personnel, intratheater aeromedical evacuation, flight medicine, preventive medicine and bioenvironmental engineering, medical aspects of the drug abuse program and the prisoner of war release program.

In April 1973 General Chesney transferred to Headquarters Tactical Air Command, Langley Air Force Base, Virginia, as command surgeon. He moved to Brooks Air Force Base, Texas, in August 1978 where he was commander of the Air Force Medical Service Center. General Chesney served as director of medical plans and resources, Office of the Surgeon General, Headquarters U.S. Air Force, from January 1980 until assuming his present position in April 1980.

General Chesney is a member of the Society of Air Force Physicians, Society of Air Force Flight Surgeons, International Congress of Medical Astronautics and Cosmonautics and Phi Rho Sigma Medical Fraternity. He is a fellow of the American College of Physicians, fellow of the American College of Preventive Medicine and diplomate of the American Board of Internal Medicine.

He holds the aeronautical rating of chief flight surgeon. His military decorations and awards include the Distinguished Service Medal, Legion of Merit, Meritorious Service Medal, Air Force Commendation Medal, Air Force Outstanding Unit Award ribbon, National Defense Service Medal and the Spanish Cross of the Aeromedical Order of Merit, 2nd Class.

He was promoted to major general February 8, 1979, with date of rank July 1, 1975.

General Chesney is married to the former Mary Ann Wilson. They have four children: Murphy A. III, Charles Allen, Carol Jean and John Lowell.

I am Major General Murphy A. Chesney, Air Force Deputy Surgeon General. I thank you for the opportunity to present an update on the progress of the Air Force Epidemiologic Study of Ranch Hand personnel exposed to herbicides in Vietnam between 1961-1971. Our previous Congressional presentations have included information on the use of herbicides in Vietnam, the development and peer review process of the Air Force study design and protocol, the process of study implementation, compliance figures, program costs and preliminary mortality findings.

The Air Force has now completed the first mortality report, and I will present the results of this baseline mortality study to you today.

Twelve hundred sixty-nine (1269) individuals who were assigned to Air Force units directly involved in Operation Ranch Hand were identified through extensive searches of military historical and personnel records. These men were generally exposed to herbicides for up to 10-12 hours a day, 5 to 6 days a week, for periods of at least one year. Thus, the Air Force considers them to be the most heavily herbicide exposed group of U.S. military personnel in Vietnam. For the purpose of statistical comparison, a group of other Air Force personnel assigned to duty in Southeast Asia was selected. They were matched to the Ranch Hand group by race, job and date of birth. Five comparison subjects were selected for each of the Ranch Handers to improve the ability of the study to detect a difference in death experience. The death experience of the herbicide/dioxin exposed group was contrasted with the death experience of the matched group, and three other groups external to this study--the 1978 U.S. white male population, a Department of Defense (DOD) retired population, and the 1956 class of West Point.

All Ranch Hand and comparison subjects designated as killed in action (KIA) were removed from the study population, leaving 1247 Ranch Handers and 6171 comparison subjects for the mortality determination. Analysis of these KIA deaths will be performed for the next annual report of mortality. As of December 31, 1982, 50 Ranch Hand and

250 comparison subjects had died (certified on/before April 27, 1983). This represents only 4% of each group. Death certificates were obtained on all 300 deceased subjects.

Of these 50 Ranch Hand deaths, there were 19-accidental deaths; 3-suicides; 2-homicides; 4-malignant neoplasms; 1-endocrine, nutritional, metabolic and immunity disorder; 16-diseases of the circulatory system; and 5-diseases of the digestive system. For the same time period, there were 250 deaths among the comparison subjects. The larger number of comparison subject deaths is a result of the 1:5 Ranch Hand to comparison subject mortality study design. The causes of death for this group include: 92-accidental deaths; 14-suicides; 3-homicides; 39-malignant neoplasms; 2-neoplasms of uncertain behavior; 1-endocrine, nutritional, metabolic and immunity disorder; 70-diseases of the circulatory system; 11-diseases of the digestive system; 3-infectious and parasitic diseases; 2-nervous system and sense organ disorders; 1-mental disorder; 4-respiratory system diseases; 3-genitourinary system conditions; 2-ill-defined conditions; and 3-unknown conditions. No statistically significant differences in the crude death rates were found between the Ranch Hand and the comparison group. There were no soft tissue sarcoma deaths diagnosed in either group.

Analysis showed that, to date, the mortality experience of the Ranch Hand group is identical to that of the matched comparison group. The overall rates and causes of death are not significantly different between the groups. However, it does appear that officers are living longer than enlisted personnel in both groups. The Ranch Handers did show a relative decrease in cancer, but an increase in liver disorder deaths; however, both of these findings are statistically nonsignificant. The sites of all cancers are shown in the following table:

SITE SPECIFIC MALIGNANT NEOPLASM MORTALITY

	Deaths	
Site ICD Code (9th Ed)	Ranch Hand	Comparison
Lip, oral cavity, Pharynx (140-149)	0	4
Digestive organs, peritoneum (150-159)	0	8
Respiratory, intrathoracic (160-165)	2	15
Bone, connective tissue, skin, breast (170-175)	0	1
Genitourinary organs (179-189)	1	4
Brain (191-192)	0	2
Lymphatic and hematopoietic tissue (200-208)	0	4
No site specification (199)	1	1
	4	39

These data are not adjusted for other medical or environmental risk factors of interest, such as length of time in Vietnam or Southeast Asia, herbicide dose, time since exposure, time in active duty military, or other nonmilitary chemical exposures. The number of cancers is small but, the morbidity data we hope to release in October will include cured cancer cases, ongoing cancer cases, and recorded cancer deaths. These data may be substantially larger and will undergo more refined analysis.

The next table presents the digestive system mortality:

DIGESTIVE SYSTEM MORTALITY

	Deaths	
ICD Code (9th Ed)	Ranch Hand	Comparison
Pancreatitis (5770)	1	2
Alcoholic cirrhosis (5712)	0	3
Nonalcoholic cirrhosis (5715)	3	3
Nonalcoholic fatty liver (5718)	0	1
Chronic liver disease (5728)	0	1
Alcoholic liver disease (5711)	1	0
Duodenal ulcer (5325)	0	1
	5	11

While these findings are preliminary and statistically nonsignificant at this time, they represent a key area of interest for continued analysis.

Analysis of both the overall Ranch Hand and the overall comparison groups to the 1978 U.S. white male mortality experience showed highly significant findings of less mortality than for equivalently aged U.S. white males. Most of these differences can be attributed to the healthy worker effect. This is due to the fact that individuals must be in basically good health upon entry into military service, while the general U.S. population is not subject to this form of "selection." The DOD retired and West Point data were used for further analyses in an attempt to better define the healthy worker effect. The contrast with the DOD data again demonstrated significantly less mortality for Ranch Hand officers, comparison officers and comparison enlisted men. The Ranch Hand enlisted group did have a favorable mortality experience, but not to a statistically significant degree. The reason(s) for these observations are speculative at present, but may include the related factors of sample size, socioeconomic differences, access to medical care, and health education and possible herbicide effects. The West Point comparison had to be restricted to an analysis of the officer groups since all West Point graduates became officers. This analysis revealed no significant differences in mortality.

In the basic analysis using the matched comparison group, a relative risk of 0.964 was found. Relative risk is the ratio of probability of death in one group (Ranch Hand) to the probability of death in another (matched comparison). If the likelihood of deaths was the same in both groups, the result would be 1; increased mortality in the Ranch Handers would result in a value greater than 1. These findings, therefore, indicated overall equivalence between Ranch Handers and their matched comparisons.

In summary, the mortality analyses described in this report have not revealed any adverse death experience in the herbicide/dioxin exposed group. The results of the analyses, regardless of the source of the comparison data, were consistent. At this time, there is no indication that Operation Ranch Hand personnel have experienced any increased mortality or any unusual patterns of death in time or by cause. They are not dying in increased numbers, at earlier ages, or by unexpected causes. However, the fact that adverse effects have not yet been detected does not imply that an effect may not become manifest at a future time. For this reason, further anlyses are intended, and mortality in the study population will be ascertained annually for the next 20 years.

The analysis of the data collected during the questionnaire and physical examination phases of the Ranch Hand Study is well underway and proceeding on schedule. The report on this aspect of the study will be reviewed by the Advisory Committee on Special Studies Related to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants. We anticipate that the report will be made available to the public in October.

I will be happy to answer questions at this time.

PROJECT RANCH HAND II

AN EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDES

BASELINE MORTALITY STUDY RESULTS

30 JUNE 1983

Prepared for:
The Surgeon General
United States Air Force
Washington, D.C. 20314

Approved for public release; distribution unlimited

EPIDEMIOLOGY DIVISION
DATA SCIENCES DIVISION
USAF SCHOOL OF AEROSPACE MEDICINE (AFSC)
BROOKS AIR FORCE BASE, TEXAS 78235

EXECUTIVE SUMMARY
Baseline Mortality Study

The Ranch Hand II epidemiologic study uses a matched cohort design in a non-concurrent prospective setting, incorporating mortality, morbidity, and follow-up studies. The purpose of this report is to present the baseline mortality study results.

Since 1979, a detailed population ascertainment process has enumerated a total of 1269 Ranch Hand personnel who served in Vietnam during the period of 1962-1971. As described in the protocol, this total is believed to comprise the entire exposed study population. The eligibility of each Ranch Hander was verified by a hand review of his personnel record. A comparison group was formed by identifying all individuals assigned to selected Air Force organizational units with a mission of flying cargo to, from, and in Vietnam during the same period. All Ranch Hand and comparison subjects designated as killed in action were removed from the study population. By a computerized nearest neighbor selection process, up to 10 comparison individuals were matched to each Ranch Hander by job category, race, and age to the closest month of birth. A hand record review of the matched comparison sets revealed that on the average, 8.2 comparison individuals were fully suitable for study. From each matched comparison set, five individuals were randomly selected for the mortality study, yielding a 1:5 design. Every Ranch Hander and his set of comparisons will be the subjects of annual mortality updates throughout the entire 20 years of the followup study so that emerging mortality patterns or disease clusters may be detected with maximal sensitivity. Each living Ranch Hander and his first and willing comparison match were selected to participate in a comprehensive physical examination and an in-home interview; the results of this study will be presented in a subsequent report in late 1983.

A mortality determination on 1,247 Ranch Handers and 6,171 comparison subjects was made, sequentially using the data sources of the Air Force, Veterans Administration, Social Security Administration, Internal Revenue Service, and personal contact efforts. As of December 31, 1982, 50 Ranch Hand and 250 comparison subjects had died (certified on/before April 27, 1983). Death certificates were obtained on all 300 deceased subjects and were coded by an Air Force nosologist (ICD, 9th ED). All codings were verified by the National Center for Health Statistics. Autopsy results are currently being sought for future analyses.

Statistical analyses of non-cause-specific death emphasized survival curve estimates, linear rank procedures, relative risk estimates, and standardized mortality ratios (SMRs). Cause specific analyses were limited to relative risk estimates because of small cell sizes. In addition to these approaches, three other data bases were contrasted to the Ranch Hand population where possible; the 1978 US White Male Mortality experience, the 1978 Department of Defense (DoD) Nondisability Retired Life Table, and the mortality experience of the West Point Class of 1956. These additional comparison groups have substantial comparability or sample size limitations, rendering conclusions to the weakest order. Analyses with these "external" comparison groups were accomplished to crudely define the healthy worker effect and to determine if the Ranch Hand group mortality was drastically out of line with that of other military populations.

Data analysis showed that the mortality experience of the Ranch Hand group is nearly identical to that of the comparison group. Analyses showed that officers are living longer than enlisted personnel in both Ranch Hand and comparison groups. This difference between officers and enlisted personnel was statistically significant in the comparison group whereas it was not in the Ranch Hand cohort. A contrast of the Ranch Hand and comparison group to the 1978 DoD Life Table showed significantly less mortality for Ranch Hand officers, comparison officers and comparison enlisted men, however, there was not a statistically significant favorable mortality rate for Ranch Hand enlisted personnel. This pattern of mortality was also seen in a contrast of the Ranch Hand and comparison groups to the 1978 U.S. white male mortality experience. That is, highly favorable mortality differentials for Ranch Hand officers, comparison officers and comparison enlisted personnel were observed, but not for Ranch Hand enlisted. This trend is consistent with the self perceptions of differential herbicide exposures reported by many of the Ranch Hand subjects. The reason(s) for these observations are speculative at present, but may include the related items of sample size, socioeconomic differences, access to medical care, and health education and possible herbicides effects. Cause specific analyses were statistically nonsignificant. The Ranch Handers showed a relative paucity of overall cancer but an excess of digestive disorder deaths, both statistically nonsignificant. No soft tissue sarcoma deaths were detected in either group. Analyses of both the Ranch Hand and the comparison groups to the 1978 US White male mortality experience showed highly significant favorable findings. Most of these differences are speculatively attributed to the healthy worker effect. A contrast of the Ranch Hand and comparison groups to the 1978 DoD Life Table showed significantly less mortality for Ranch Hand officers and comparison officers and enlisted men. The West Point comparison showed nonsignificant SMRs of 0.530 and 0.778 for the Ranch Hand officers and the comparison group officers respectively. Overall, the limitations of the statistical power calculations in most of these analyses were substantial in most analyses due to 1) the low mortality rate (4%) in the Ranch Hand and comparison groups to date, 2) the inherently small group of Ranch Handers (as described in the study protocol), and 3) the observed relative risks which approached unity in most categories.

This baseline mortality report can in no way be regarded as conclusively negative because this small, young, and relatively healthy cohort may not have yet reached the latency period wherein attributable fatal disease might be expected and detected within limited power boundaries of this study. Future commitments for the annual mortality updates include detailed covariate analyses for disease risk factors, herbicide exposure, and confounding industrial chemical exposures. Further, subsequent morbidity reports will include full spectrum, disease specific analyses, e.g., cancer (fatal, ongoing, cured) in an effort to enhance study sensitivity to emerging herbicide effects, if they occur.

PREFACE

In October 1978 the United States Air Force (USAF) Surgeon General made the commitment to the Congress and to the White House to conduct an epidemiologic study of the possible adverse health effects arising from the herbicide exposure of Air Force personnel who conducted aerial dissemination missions in Vietnam (Operation Ranch Hand). The purpose of this epidemiologic investigation is to determine whether long-term adverse health effects exist, and whether they can be attributed to occupational exposure to herbicides and their contaminants. The study protocol (1) for this effort incorporates a matched cohort design placed in a non concurrent prospective setting. The study approach includes mortality, morbidity, and follow-up elements linked tightly in time in order to produce the most data in the shortest period of time. The study addresses the question: Has there been, or are there currently, or will there be any adverse health effects among former Ranch Hand personnel caused by repeated occupational exposure to 2,4,5-T containing herbicides and the contaminant, TCDD? At the request of the Principal Investigators (See appendix I) the study protocol was extensively and independently peer reviewed. The review agencies included: The University of Texas School of Public Health, Houston Texas, the USAF Scientific Advisory Board, the Armed Forces Epidemiological Board, and the National Research Council of the National Academy of Sciences. In 1980, the Science Panel of the Agent Orange Working Group was created as an additional peer review agency. This group, redesignated as the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants, has consented to the oversight responsibility of the Ranch Hand study and continues to monitor the conduct of this epidemiologic investigation (See Appendix II). The approved and official protocol for this effort is available to the public through the National Technical Information Services.

The Ranch Hand II Study protocol heralds the suboptimal statistical power of the mortality study. The mortality study was motivated by the desire to use a full spectrum epidemiologic approach to the herbicide question. Additionally, the investigators were scientifically obliged to pursue the mortality study because of previous and emerging studies (some with small sample sizes) which suggested the possibility of a soft tissue sarcoma endpoint (2,3,4). Within the inherent sample size limitation of the Ranch Hand population, detection of such a rare condition will be missed unless there is marked case clustering and correspondingly high relative risks.

Also because of sample size limitations as well as the myriad of proposed clinical endpoints, a case-control design was not entertained. The investigators have attempted to enhance statistical power and analytic sensitivity where possible by using 1) a large comparison group, 2) precise matching procedures, 3) annual mortality updates, 4) mortality-morbidity linkages, 5) a lengthy follow-up study, 6) external comparison groups, and 7) state-of-the-art statistical methodology. A final assessment of overall mortality must necessarily await substantially more data and covariate approaches to identify and isolate unusual emerging mortality patterns if they occur.

This report is primarily directed to individuals with statistical and epidemiologic backgrounds. It also assumes that the reader has a familiarity with the herbicide/dioxin issue and a detailed knowledge of the protocol of the Air Force study. In the interest of brevity, the reader is referred to the protocol published as US Air Force School of Aerospace Medicine Technical Report 82-44. This report is available from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161.

Chapter I

THE MORTALITY STUDY DESIGN

1. The Study Population

The exposed study population, termed "Ranch Hand", was defined as those individuals who were formally assigned to the USAF organizations responsible for the aerial dissemination of herbicides and insecticides in the Republic of Vietnam from 1962 to 1971. These individuals were identified from historical data sources at the National Personnel Records Center (NPRC), St. Louis, Missouri and the USAF Human Resources Laboratory, Brooks Air Force Base, Texas. A total of 1,269 Ranch Hand personnel were eventually identified through this process. The comparison population was defined as those individuals who were assigned to a variety of cargo mission organizations throughout Southeast Asia during the same time period. Cargo mission air crew members and support personnel were selected because of sufficient population size, similar training and military background experiences, and psychologic similarities to the Ranch Hand group. The comparison population was not occupationally exposed to herbicides or insecticides in the Republic of Viet Nam. Identification of this population was completed using the same historical data sources as were used with the Ranch Hand population; 24,971 individuals were so identified. In preparation for matching the study and comparison populations, all subjects killed in action (KIA) were removed from the data base. The rationale for this action is the assumption that combat death in the Ranch Hand group was not caused by the immediate effects of herbicide exposure; KIA's were removed from the comparison group for comparability purposes. A KIA analysis will be performed in a subsequent report. The Ranch Hand KIA subgroup, numbering 22 individuals, although not matched, was maintained in the data base but were deleted from the mortality analysis, leaving 1247 Ranch Hand subjects.

The Ranch Hand population was matched to the comparison population with an iterative nearest-neighbor computer program (1). Up to 10 comparison subjects were matched to each Ranch Hander by year of birth, race (Black versus non-Black), and occupational category (officer pilot, navigator and other; enlisted flight engineer and other), thus creating matched sets of one study subject and up to 10 comparison subjects. All subjects are males. The mean age of the study subjects is 45 years.

Following the original match, the majority of Ranch Handers had 10 comparisons. The exceptions were the group of non-Black pilots who had a mean of only 9.5 comparisons per exposed subject due to the extreme ages of several individuals, and the strata of Black pilots and other Black officers who only had means of 2.7 and 5.0, respectively. In December, 1981, the USAF Principal Investigators learned that several morbidity study comparison subjects had reported no experience in Southeast Asia, suggesting that overselection of the comparison population had occurred (1). Manual review of the comparison subjects' military personnel records revealed that 18 percent of the 12,193 comparison individuals in the original match were ineligible for study. The inadvertent inclusion of several non-Southeast Asia organizations resulted in the selection of these inappropriate individuals. These ineligible subjects were found to be randomly distributed throughout the matched sets and were removed from the study. Following the removal of the ineligible subjects, the study was reduced to a 1:8 design. Also during this period, five Ranch Hand subjects were identified through personnel record sources and Veterans Administration Education Benefits and Financial Records. These five individuals had not been identified earlier because the majority of their military personnel records had been destroyed in a fire at the NPRC in St. Louis. Three of these five were newly found Ranch Handers and two were comparisons subsequently identified as Ranch Handers. No attempt was made to match comparisons to these five new Ranch Handers. During the removal of ineligible subjects, one Ranch Hander, a Black officer pilot, lost his only comparison and remains unmatched, giving a total of six unmatched Ranch Handers. All six of these unmatched Ranch Handers, are included in the morbidity and mortality studies. They were used in the analyses where appropriate, in order to improve statistical power.

2. The Mortality Population

Five comparisons per exposed subject were considered more than adequate for mortality analyses; this estimate has recently been verified under a multiplicative model by Breslow, et al. (5). Up to five comparisons in each match set, were identified from the 1:8 cohort as the mortality comparisons. Since the positions of the individuals in the match sets had already been randomized in the data file, the selection of the first five positions in each match set array for membership in the mortality comparison resulted in a random selection of the mortality comparison cohort. If a Ranch Hander had at least one but no more than five comparisons after removal of the ineligibles, then all of his matched set were used in the mortality component of this study. The mortality population is, therefore, defined as the 1241 matched Ranch Handers and their randomly chosen mortality comparisons (6171 individuals) and the six unmatched Ranch Handers. Table 1 summarizes the mortality population by occupational category and race. Here, and elsewhere in this report, non-Black is defined as Caucasian, Mexican or Oriental.

Table 1

MORTALITY POPULATION SUMMARY BY OCCUPATION AND RACE

Occupation, Race	Counts Ranch Hand	Counts Comparison
Officer-Pilot, Non-Black	349	1740
Officer-Pilot, Black	6	13
Officer-Navigator, Non-Black	80	390
Officer-Navigator, Black	2	10
Officer-Other, Non-Black	25	123
Officer-Other, Black	1	2
Enlisted-Flt Eng, Non-Black	189	935
Enlisted-Flt Eng, Black	15	75
Enlisted-Other, Non-Black	528	2628
Enlisted-Other, Black	52	255
	1,247	6171

The overall match ratio, 6171/1247=4.95, reflects the lack of suitable controls in some strata, the subsequent removal of ineligible comparisons and the addition of five unmatched Ranch Handers. A detailed description of the matching results is given in Appendix III.

Those Ranch Handers having fewer than five matched mortality controls are summarized in Table 2.

Table 2

RANCH HAND SUBJECTS WITH LESS THAN FIVE COMPARISON SUBJECTS

	Counts		
Occupation, Race	Ranch Hand	Comparisons[3]	Notes
Officer-Pilot, Non-Black	1	2	1
	1	3	1
Officer-Pilot, Black	1	0	1
	1	1	1
	2	2	1
	1	3	1
Officer-Navigator, Non-Black	2	0	2
Officer-Other, Non-Black	2	4	1
Officer-Other, Black	1	2	1
Enlisted-Flt Eng, Non-Black	2	0	2
Enlisted-Other, Non-Black	12	4	1
Enlisted-Other, Black	1	0	2
	27		

Note 1. Lack of suitable comparison subject or loss due to ineligibility.
Note 2. New Ranch Hander, no attempt to match.
Note 3. Comparisons per Ranch Hander

Chapter II

THE MORTALITY DETERMINATION PROCESS

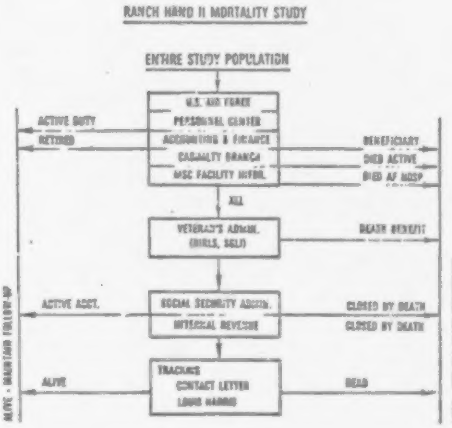
1. Introduction

The mortality status of the Ranch Hand group and their mortality comparisons are, and will continue to be, ascertained using four major data sources: USAF, Veterans Administration (VA), other Governmental and morbidity population tracking. The mortality determination process using these data sources is presented in Figure 1.

Figure 1.

RANCH HAND II

MORTALITY DETERMINATION ALGORITHM


RANCH HAND II MORTALITY STUDY
ENTIRE STUDY POPULATION
U.S. AIR FORCE
PERSONNEL CENTER
ACCOUNTING & FINANCE
CASUALTY BRANCH
MSC FACILITY INFOR.
ACTIVE DUTY
RETIRED
BENEFICIARY
DIED ACTIVE
DIED AF HOSP
ALL
VETERAN'S ADMIN.
(BIRLS, SGLI)
DEATH BENEFIT
SOCIAL SECURITY ADMIN.
INTERNAL REVENUE
ACTIVE ACCT.
CLOSED BY DEATH
CLOSED BY DEATH
TRACKING
CONTACT LETTER
LOUIS HARRIS
ALIVE
DEAD
ALIVE - MAINTAIN FOLLOW-UP
DEAD - REQUEST DEATH CERTIFICATE

The entire study population was matched or checked against the first three sections of this algorithm while only the morbidity population was contacted and tracked. A description of the data sources within the algorithm follows.

2. United States Air Force Data Sources

The USAF data sources include the USAF Military Personnel Center (MPC) records, the USAF Accounting and Finance Center records, and the USAF Medical

Service Center Facility Use Data. The USAF MPC records include the individual's military personnel record and the data accumulated by the Casualty Branch of the MPC. Individual military personnel records are created at the time of induction into the USAF, and reflect a chronological history of the individual's military career. Epidemiologically, these records are an invaluable data source as they can be used for the development of occupational histories, identification of race, sex, and date of birth as well as for location of personnel, and for determining vital status. Hard copy records of these data are maintained at the individual's base of assignment while on active duty; a computer copy of these records is maintained at the USAF military personnel center, Randolph AFB, Texas. Following retirement and/or separation from the USAF, these records are forwarded to the National Personnel Records Center (NPRC), St Louis, Missouri, the record repository for all military personnel records. They are indexed by Social Security Account Number or Air Force Serial Number at the NPRC. If an individual should die while on active duty, after retirement, or within 120 days of separation from active duty, it is the responsibility of the Casualty Branch of the USAF Military Personnel Center to update the hard copy military personnel record and the MPC computer data base and to inform the USAF Accounting and Finance Center of this fact. At the same time, USAF MPC personnel initiate a copy of the USAF Form 1312, Report of Retired Casualty, or Department of Defense DD Form 1300, Report of Casualty. The selection of the appropriate form is based on the current status of the individual concerned. The DD Form 1300 also clarifies an individual's casualty status which can be either battle or non-battle. Copies of the appropriate death form are sent to appropriate agencies while the original is placed in the individual's military personnel record.

Since the initial review of military personnel records, a system has been established with the Casualty Branch of the Military Personnel Center wherein all active duty and retired death forms are forwarded monthly to the Occupational Epidemiology Section of the USAF School of Aerospace Medicine Epidemiology Division. In this way, the mortality status of all active duty and retired study subjects is systematically determined on a continuing basis.

The USAF Accounting and Finance Center data base was used as a resource to update individual Air Force serial numbers to Social Security numbers. The Social Security number is required for all other aspects of the mortality algorithm.

The Air Force Medical Service Center (AFMSC) Facility Use Data is a computer data base containing information regarding all active duty and retired deaths that occur in Department of Defense (DOD) Medical Facilities. This data base identified no additional deaths in the mortality population, but did verify the deaths known to have occurred in DOD hospitals.

In addition to the USAF data bases, the Ranch Hand Association, a reunion association of approximately 850 Ranch Handers, has contributed to the success of this study. This group has assisted the Principal Investigators in the ascertainment of the exposed population, and in the determination of the current location and the mortality status of the group. The association contacts all of its members yearly through newsletters and provides updated information to the Air Force investigators.

3. Veterans Administration Death Beneficiary Identification and Record Location Subsystem

The Beneficiary Identification and Record Locator Subsystem (BIRLS) is a Veterans Administration data base generated by the Veterans Administration for determination of funeral allowance. If the family of the deceased informs the funeral director that the deceased served in the US military, the funeral director submits the required data to the Veterans Administration. In January 1981, August 1982, and January 1983, the BIRLS data base was searched for Ranch Hand and comparison deaths. In addition to these searches, the Department for Veterans Benefits, Veterans Administration, coordinated the gathering of death certificates from VA regional offices.

4. Other Governmental Data Sources

A. Internal Revenue Service

Public Law 96-126, Section 502, 28 November 1979, authorized the use of Internal Revenue Service (IRS) addresses for individuals who had been exposed to occupational hazards in order to determine the status of their health. The National Institute for Occupational Safety and Health (NIOSH) coordinated the USAF requests for these IRS addresses. This system is based on the address shown on individual tax returns and is corrected once a year. The addresses are verified by NIOSH through use of a post card mailed to the post office responsible for the individual's mail delivery. NIOSH assumes that the individual is alive if he files a tax return and if the verification scheme confirms his address for mail delivery. The IRS assumes an individual is dead if the individual is so reported on a joint tax return. The IRS data base search provides an incomplete mortality determination, however, since absence of an individual tax return does not necessarily imply death of that individual.

B. Social Security Administration

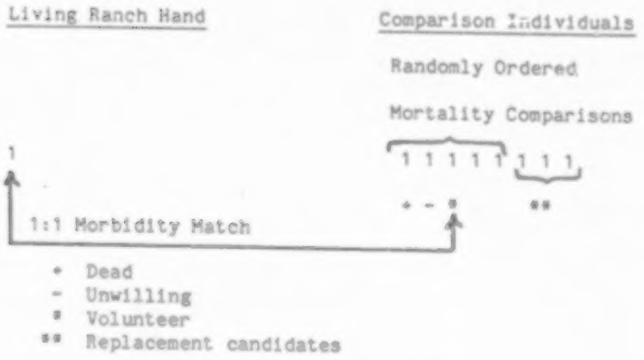
The Social Security Administration (SSA) is a source of mortality information based on data maintained by the Office of Remuneration and Earnings. The basis for this data is employer-reported earnings. The SSA assumes that an individual is living if there is no indication of death on the individuals record and earnings are recorded for the last calendar year or retirement, disability, black lung or supplemental security income payments are being made. The SSA did inform us that they do not conduct an exhaustive search, and all deaths are not necessarily reported to SSA. Therefore, this mortality information may not be complete.

5. Morbidity Population Tracking

Individual tracking techniques apply only to the morbidity population, defined as those selected and compliant to questionnaire. The morbidity population for this effort is defined as all Ranch Handers and their morbidity comparisons. The morbidity comparisons are, in general, also mortality comparisons. The selection procedure for the morbidity study is presented in Figure 2.

Figure 2.

SELECTION PROCEDURE FOR THE QUESTIONNAIRE PHYSICAL EXAMINATION, AND FOLLOW-UP STUDY



In this figure, the first randomly ordered comparison was found to be dead. The second was contacted but was unwilling to participate and the third volunteered to participate in the questionnaire component of the morbidity effort. This contacting process for the morbidity effort was the final step in the baseline mortality determination. The original contact was made by certified mail. Each Ranch Hander and a random living comparison was sent an introductory letter and fact sheet signed by the USAF Surgeon General. A Louis Harris and Associates (LHA) interviewer then accomplished an in-home interview.

LHA identified two Ranch Handers and nine comparisons who could not be located. All eleven unlocatable subjects were assumed living and remain included in the mortality study.

6. Receipt and Coding of Death Certificates

Death certificates were ordered from the vital statistics department of the appropriate state, trust territory, or foreign country. Death certificates or their equivalent were obtained on all appropriate subjects.

All death certificates were coded by two individuals, trained by the National Center for Health Statistics (NCHS) in underlying and multiple cause of death coding procedures, using the International Classification of Diseases, Ninth Edition (1977) coding system. Classification of the underlying cause of death was in accordance with NCHS decision tables. Each coder independently classified the underlying and multiple causes of death and gave the coding worksheet, with each corresponding death certificate, to the coding supervisor, a trained nosologist, for reconciliation. Following reconciliation, one of the coders placed the death code information, by computer terminal, in the death certificate mortality file via a software program designed to mimic the NCHS underlying multiple cause of death coding sheet. At the conclusion this initial input of the death codes, a copy of the death certificate was forwarded to NCHS for further validation. The NCHS returned coded death certificates, which were then compared with the Air Force classification. Discordances were resolved in cooperation with NCHS and entered into the data base.

7. Results

Chapter II has reviewed the comprehensive, cohesive, sequential ascertainment process of death in the study populations. This process has resulted in the identification of 50 dead Ranch Hand subjects and 250 dead comparison subjects. Although it is understood that early differential ascertainment occurred in the Ranch Hand members (because of detailed knowledge of the study group), it is judged that the overall comprehensive ascertainment process is currently balanced with respect to the two groups.

Table 3 and Appendix IV contain summary counts by age, job, and race category for all Ranch Handers and their mortality comparisons; these counts reflect mortality as of 31 December 1982, as known on 27 April 1983. In the stratified analyses,the term "at risk" is defined as simply the number of subjects within a specific stratum, and in life table analyses, as the number of subjects entering a specific age bracket. The term "rate" is the proportion of those individuals "at risk" who are dead.

Table 3

OCCUPATIONAL AND RACE SPECIFIC MORTALITY

Race	Occupation	Ranch Hand			Comparisons		
		At Risk	Dead	Rate	At Risk	Dead	Rate
Non-Black	Officer-pilot	349	12	.034	1740	72	.041
	Officer-navigator	80	2	.025	390	13	.033
	Officer-other	25	1	.040	123	3	.024
	Enlisted-flt eng	189	6	.032	935	46	.049
	Enlisted-other	528	25	.047	2628	97	.037
Black	Officer-pilot	6	0	.000	13	0	.000
	Officer-navigator	2	0	.000	10	0	.000
	Officer-other	1	0	.000	2	0	.000
	Enlisted-flt eng	15	2	.133	75	9	.120
	Enlisted-other	52	2	.038	255	10	.039
	TOTAL	1247	50	.040	6171	250	.041

Chapter III

RANCH HAND VERSUS COMPARISON GROUP ANALYSES

1. Introduction

Overall survival comparisons, without regard to cause of death, were made via survival curve estimation, linear rank procedures, relative risk estimation and standardized mortality ratios. Survival curves were estimated and plotted using the method of Kaplan and Meier (6); 95% confidence bands (7) for each survival curve estimate were also plotted on each graph. Linear rank testing was carried out using the logrank test and Prentice's censored data extension of the Wilcoxon test (8). All linear rank tests were carried out with match sets merged when Ranch Hands differed by less than one year relative to date of birth, within each stratum of job and race (9). These merged match sets were regarded as separate strata for testing purposes(9, 10, 11). Relative risk estimates and confidence intervals were computed using an extension of the method of Ejigou and McHugh (12) to variable length, one-to-many match sets (see Appendix V). Here, due to the one-to-many limitation of the algorithm, match sets were not merged as when testing procedures were performed. Standardized mortality ratios and associated tests and plots were carried out as in Gail (13).

These analyses are fully adjusted for the matching variables, age, race and occupation, but are unadjusted for other variables of interest, such as length of time in Vietnam or Southeast Asia, herbicide dose, time since exposure, time in active duty military, and other medical or occupational risk factors. Some of these variables, such as herbicide dose and time since exposure will be adjusted for in the next analyses, after such data become available. In particular, latency analyses cannot be undertaken at this time but will be included in the next mortality report.

In these analyses, we have used summary statistics for which underlying modeling assumptions can be tested. For this reason, we have used the Breslow-Day (13) approach to SMR calculation, rather than the more traditional person-years method. A detailed explanation of this choice is given in Chapter VI.

2. Overall Comparisons

Survival time in these analyses was regarded as independent of censorship, if any, and was taken to be age at death. All subjects not certifiably dead, as of 31 December 1982, at the time of analysis, were considered censored at their age on that date. Contact has been lost with two Ranch Handers and nine comparisons as described in Chapter II, but these are not assumed lost to follow-up for the purpose of mortality determination. They are assumed to have been alive on 31 December 1982. With this assumption, no subjects were lost to mortality follow-up before 31 December 1982 in this study.

Ranch Hand and comparison group survival curve estimates and their associated 95% confidence bands are shown in Figure 3 and Appendix VI for the five groups: pooled, officers, enlisted, flying and ground personnel, as defined in Table 4. The curves for the pooled groups are shown in Figure 3 with the 95% confidence interval bands deleted in the interest of legibility, but they are included in the group specific curves in Appendix VI. Review of

Ranch Hand operations has strongly suggested that Ranch Hand enlisted personnel were more heavily exposed to herbicide than Ranch Hand officers. Further, there is a perception of possible exposure differential between flying and ground Ranch Hand personnel. These notions prompted the above groupings and analyses seen in this and subsequent chapters. Analyses of latency are not possible at this time due to the as yet incomplete nature of the military service database. These analyses will be performed after the hand review of military tour records has been completed.

Figure 3

SURVIVAL CURVE ESTIMATES FOR POOLED RANCH HANDERS AND COMPARISON SUBJECTS

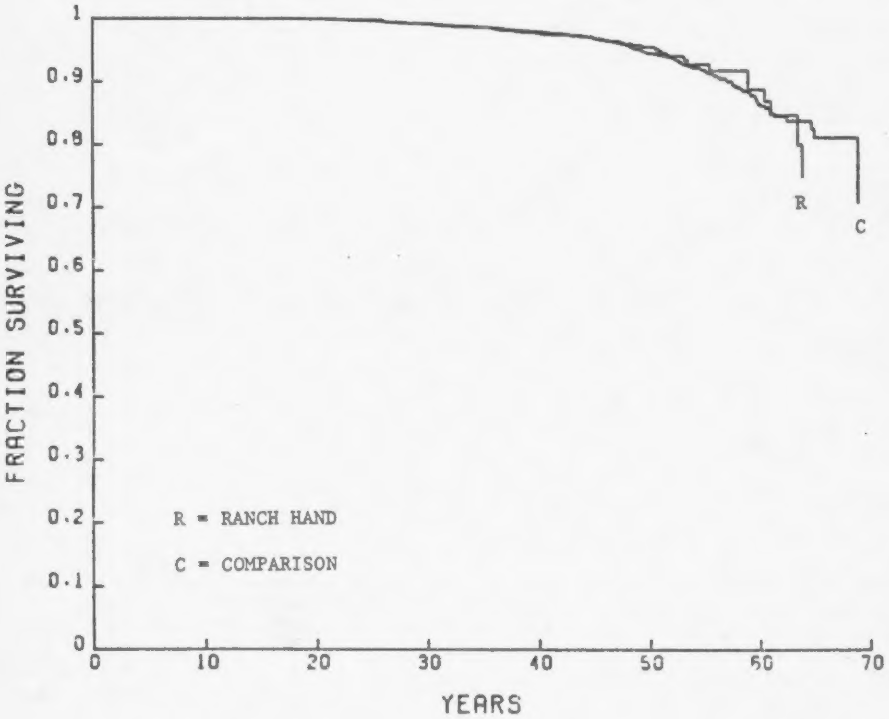


Table 4

GROUP DEFINITIONS

Group	Definition
Officer	Officer-pilot, navigator, other
Enlisted	Enlisted-flight engineer, other
Flying	Officer-pilot, navigator Enlisted-flight engineer
Ground	Officer-other Enlisted-other
Pooled	All occupational categories

Summary counts by group are shown in Table 5. Ignoring the matching, interaction between officer-enlisted categories and Ranch Hand membership, and interaction between flying-ground categories and Ranch Hand membership was evaluated using log-linear models. No statistically significant interactions were detected.

Table 5

SUMMARY COUNTS BY GROUP

	Ranch Hand			Comparisons		
Group	At Risk	Dead	Rate	At Risk	Dead	Rate
Officer	463	15	.032	2278	88	.039
Enlisted	784	35	.045	3893	162	.042
Flying	641	22	.034	3163	140	.044
Ground	606	28	.046	3008	110	.037
Pooled	1247	50	.040	6171	250	.041

Linear rank procedures were carried out on the same five groups. The results, summarized by test statistics and two-sided P-values, are shown in Table 6. Small P-values, less than .05, indicate significant differences, at the 5% level, between the two groups. These procedures are designed so that the statistic will be positive when the Ranch Handers are dying before the comparison subjects and negative when the comparisons are dying prior to the Ranch Handers. The null hypothesis is that the actual survival distributions of Ranch Handers and their matched comparisons are identical. Each statistic is approximately null distributed as a standard normal random deviate.

Table 6

TEST RESULTS AND P-VALUES FOR OVERALL COMPARISONS

Group	Logrank (Value)	Logrank P-Value	Wilcoxon (Value)	Wilcoxon P-Value
Officer	(-0.634)	.526	(-0.722)	.470
Enlisted	(0.383)	.702	(0.331)	.741
Flying	(-1.021)	.307	(-1.116)	.264
Ground	(1.023)	.306	(0.950)	.342
Pooled	(-0.047)	.962	(-0.123)	.902

There is no significant difference, based on these data, between the Ranch Handers and their mortality comparison group. This means that, in particular, the mean ages-at-death of the Ranch Handers and their matched comparisons are not significantly different. In some groups, pooled, officer and flying, the statistics are negative, indicating that the Ranch Handers are living longer than the comparisons, but the differences are, again, insignificant, as evidenced by the large P-values. The situation is reversed for enlisted and ground personnel. These findings are consistent with the observation that, within each group, the comparison confidence bands are contained within the Ranch Hand confidence bands. When match sets are stratified by five year intervals on year of birth, the same procedures give larger P-values than those in Table 6.

Relative risk estimates, the associated 95% confidence intervals, two sided P-values for testing the null hypothesis of relative risk equal to unity and the associated power are given in Table 7. Here, the power of the test is defined as the conditional probability of rejecting the null hypothesis at the 5% level of significance, given that the relative risk is equal to its estimated value.

Table 7

RELATIVE RISKS AND 95% CONFIDENCE INTERVALS, P-VALUES AND POWER

Group	Relative Risk	95% Confidence Interval	P-Value	Power
Officer	0.763	(.320 - 1.207)	.373	.105
Enlisted	1.065	(.660 - 1.471)	.742	.072
Flying	0.734	(.387 - 1.081)	.211	.197
Ground	1.232	(.694 - 1.769)	.337	.195
Pooled	0.964	(.658 - 1.269)	.819	.051

The confidence intervals and P-values in Table 7 indicate no significant difference, at the 5% level, between the mortality of the Ranch Handers and comparisons in each of the five groups.

Year-of-birth specific mortality rates for each of the five groups are given in Tables 8 through 12, with the corresponding standardized mortality ratios (SMR). In each group, the comparisons are the internal standard. The SMR estimates relative risk in these comparisons if the year-of-birth specific relative risks are all equal (13). A likelihood ratio test for the hypothesis of equal year-of-birth specific relative risks was carried out for each comparison; its P-value is denoted by P1. In addition, the hypothesis that relative risk is unity, given that relative risk is constant across strata, was tested via a likelihood ratio procedure (13); its P-value is denoted by P2. The SMR and both P-values are given with each comparison.

Here, and elsewhere in this report, the denominator of the SMR is $\sum n_{ij}P_i$, where n_{ij} is the number of individuals for the ith stratum of the jth population and P_i is the death rate, per person, in the standard population for the ith stratum. In these calculations the data is stratified on year of birth.

Table 8

POOLED SPECIFIC MORTALITY RATES BY YEAR OF BIRTH
(SMR = .996; P1=.389, P2=.955)

Birth	Ranch Handers			Comparison		
Year	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-14	5	2	.400	14	2	.143
1915-19	17	4	.235	96	11	.115
1920-24	48	3	.063	241	24	.100
1925-29	84	2	.024	501	40	.080
1930-34	304	15	.049	1389	67	.048
1935-39	207	7	.034	1020	33	.032
1940-44	208	5	.024	1096	23	.021
1945-54	374	12	.032	1814	50	.028
		50			250	

Table 9

OFFICER SPECIFIC MORTALITY RATES BY YEAR OF BIRTH
(SMR = .827; P1=.233, P2=.490)

Birth Year	Ranch Hand Officers			Comparison Officers		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1910-24	41	3	.073	205	17	.083
1925-34	194	4	.021	930	49	.053
1935-39	93	4	.043	458	11	.024
1940-44	90	2	.022	495	6	.012
1945-49	45	2	.044	190	5	.026
		15			88	

Table 10

ENLISTED SPECIFIC MORTALITY RATES BY YEAR OF BIRTH
(SMR = 1.074; P1=.733, P2=.722)

Birth Year	Enlisted Ranch Handers			Enlisted Comparisons		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-14	4	2	.500	12	2	.167
1915-19	9	1	.111	54	7	.130
1920-24	16	3	.188	80	11	.138
1925-29	41	2	.049	211	22	.104
1930-34	153	11	.072	749	36	.048
1935-39	114	3	.026	562	22	.039
1940-44	118	3	.025	601	17	.028
1945-54	329	10	.030	1624	45	.028
		35			162	

Table 11

FLYING SPECIFIC MORTALITY RATES BY YEAR OF BIRTH
(SMR = .769; P1=.678, P2=.238)

Birth Year	Flying Ranch Handers			Flying Comparisons		
	At Risk	Dead	Rate	At Risk	Dead	Rate
1915-24	44	4	.091	220	23	.105
1925-34	272	8	.029	1316	71	.054
1935-39	142	6	.042	698	22	.032
1940-44	120	2	.017	653	14	.021
1945-49	63	2	.032	276	10	.036
		22			140	

Table 12

GROUND SPECIFIC MORTALITY RATES BY YEAR OF BIRTH
(SMR = 1.257; P1=.535, P2=.302)

Birth Year	Ground Ranch Handers At Risk	Ground Ranch Handers Dead	Ground Ranch Handers Rate	Ground Comparisons At Risk	Ground Comparisons Dead	Ground Comparisons Rate
1905-14	5	2	.400	14	2	.143
1915-24	21	3	.143	117	12	.103
1925-29	31	2	.065	151	19	.126
1930-34	85	7	.082	423	17	.040
1935-39	65	1	.015	322	11	.034
1940-44	88	3	.034	443	9	.020
1945-54	311	10	.032	1538	40	.026
		28			110	

These SMR comparisons are in agreement with the preceding relative risk and linear rank analyses; there is no significant difference in mortality, based on these data, between the Ranch Hand group and the comparison group.

3. Noncause Specific Occupational Comparisons

Within-group comparisons by occupation via SMR's, with P-values for testing constant relative risk across year of birth strata (P1) and for testing relative risk equal to unity (P2) are given in Tables 13 through 16. The enlisted and ground personnel are the internal standards in these comparisons. Comparisons via the logrank procedure are given in Table 17.

Table 13

RANCH HAND OFFICERS VERSUS RANCH HAND ENLISTED
MORTALITY BY YEAR OF BIRTH
(SMR = .544; P1=.280, P2= .087)

Birth Year	Ranch Hand Officers At risk	Ranch Hand Officers Dead	Ranch Hand Officers Rate	Ranch Hand Enlisted At Risk	Ranch Hand Enlisted Dead	Ranch Hand Enlisted Rate
1905-24	41	3	.073	29	6	.207
1925-34	194	4	.021	194	13	.067
1935-39	93	4	.043	114	3	.026
1940-44	90	2	.022	118	3	.025
1945-54	45	2	.044	329	10	.030
		15			35	

Table 14

RANCH HAND FLYING PERSONNEL VERSUS RANCH HAND GROUND PERSONNEL MORTALITY BY YEAR OF BIRTH (SMR = .581; P1=.382, P2=.100)

Birth	Ranch Hand Fliers			Ranch Hand Ground		
Year	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-24	44	4	.091	26	5	.192
1925-34	272	8	.029	116	9	.078
1935-39	142	6	.042	65	1	.015
1940-44	120	2	.017	88	3	.034
1945-54	63	2	.032	311	10	.032
		22			28	

Table 15

COMPARISON GROUP OFFICERS VERSUS COMPARISON GROUP ENLISTED MORTALITY BY YEAR OF BIRTH (SMR = .697; P1=.640, P2=.015)

Birth	Comparison Officers			Comparison Enlisted		
Year	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-19	44	4	.091	66	9	.136
1920-24	161	13	.081	80	11	.138
1925-29	290	18	.062	211	22	.104
1930-34	640	31	.048	749	36	.048
1935-39	458	11	.024	562	22	.039
1940-44	495	6	.012	601	17	.028
1945-54	190	5	.026	1624	45	.028
		88			162	

Table 16

COMPARISON FLYING PERSONNEL VERSUS COMPARISON GROUND MORTALITY BY YEAR OF BIRTH (SMR = .930; P1=.305, P2=.867)

Birth	Comparison Fliers			Comparison Ground		
Year	At Risk	Dead	Rate	At Risk	Dead	Rate
1905-19	45	6	.133	65	7	.108
1920-24	175	17	.097	66	7	.106
1925-29	350	21	.060	151	19	.126
1930-34	966	50	.052	423	17	.040
1935-39	698	22	.032	322	11	.034
1940-44	653	14	.021	443	9	.020
1945-54	276	10	.036	1538	40	.026
		140			110	

Table 17

LOGRANK WITHIN GROUP COMPARISONS

Comparison	Logrank	P-Value
RH Officer vs RH Enlisted	-1.468	0.142
RH Flyers vs RH Ground	-1.455	0.146
Comparison Officer vs Comp Enlisted	-2.597	0.009
Comparison Flyers vs Comp Ground	-0.363	0.717

The SMR and logrank analyses are somewhat in agreement, with both procedures finding significant differences between comparison officers and comparison enlisted, with the officers living longer. The two methods approximately agree on the Ranch Hand fliers versus ground personnel and on Ranch Hand officer versus enlisted personnel with the logrank result near significance at the .10 level; the fliers appear to be living longer than the ground personnel within the Ranch Hand group.

4. Cause Specific Ranch Hand Versus Comparison Mortality

Cause specific mortality, relative risks, two sided P-values for testing relative risk equal to unity, power and 95% confidence intervals for relative risks are summarized in Table 18 for the 1241 matched Ranch Handers and their mortality comparisons. Mortality data for the six unmatched Ranch Handers were not used in this analysis. Of the six, one has died of an accident and the rest are still alive. In some categories, the data were too sparse for relative risk estimation.

Table 18

CAUSE SPECIFIC MORTALITY AND RELATIVE RISKS

Cause	Dead		Relative Risk	95% Conf Int.	P-value	Power
	RH	Comparison				
Accidental	18	92	.959	(.466 - 1.453)	.875	.047
Suicide	3	14	1.071	(0 - 2.407)	.913	.061
Homicide	2	3	3.333	(0 - 9.297)	.099	.489
Infectious, Parasitic	0	3				
Malignant Neoplasm	4	39	.503	(0 - 1.024)	.205	.153
Uncertain Neoplasm	0	2				
Endocrine	1	1	5.000	(0 -18.859)	.102	.562
Mental Disorder	0	1				
Nervous System	0	2				
Circulatory	16	70	1.002	(.411 - 1.594)	.994	.050
Respiratory	0	4				
Digestive	5	11	2.273	(0 - 4.675)	.085	.457
Genitourinary	0	3				
Ill Defined	0	2				
Unknown	0	3				
	49	250				

The low powers in Table 18 reflect the sparseness of data or the fact that some of the observed relative risks approach unity. However, two categories do stand out as deserving further attention: malignant neoplasms and digestive system deaths. It should be noted that if matched sets are ignored and relative risk is estimated using the method of Mantel and Haenszel (14), these results remain essentially unchanged; using this approach, the relative risk for malignant neoplasms, for example, is .506 with a P-value of .195 and power equal to .254. The 95% confidence interval for relative risk using this approach is .180 to 1.419. The Mantel-Haenszel relative risk for the digestive system comparison is 2.254, with a P-value of .132 and a power equal to .325; the 95% confidence interval for relative risk is .782 to 6.501. The digestive system deaths are further defined in Table 19. There has been an increase in deaths due to liver disease among the Ranch Handers; however, this observed difference is not statistically significant. These data are also based on death certificate diagnoses, they and will be subjected to verification and validation from medical record and autopsy reports. When all deaths from liver disease are considered as a whole, a relative risk of 2.50 is found, with a 95% confidence interval of 0 to 5.501. The P value is 0.083. Similarly, the relative risk for pancreatitis is 2.50 with a 95% confidence interval of 0 to 8.501.; the P value is 0.386. These observations are of interest and will be pursued in depth in subsequent reports.

Table 19

DIGESTIVE SYSTEM MORTALITY

ICD Code (9th Ed)	Deaths	
	Ranch Hand	Comparison
Pancreatitis (5770)	1	2
Alcoholic cirrhosis (5712)	0	3
Nonalcoholic cirrhosis (5715)	3	3
Nonalcoholic fatty liver (5718)	0	1
Chronic liver disease (5728)	0	1
Alcoholic liver disease (5711)	1	0
Duodenal ulcer (5325)	0	1
	5	11

Table 20

SITE SPECIFIC MALIGNANT NEOPLASM MORTALITY

Site ICD Code (9th Ed)	Deaths	
	Ranch Hand	Comparison
Lip, oral cavity, Pharynx (140-149)	0	4
Digestive organs, peritoneum (150-159)	0	8
Respiratory, intrathoracic (160-165)	2	15
Bone, connective tissue, skin, breast (170-175)	0	1
Genitourinary organs (179-189)	1	4
Brain (191-192)	0	2
Lymphatic and hematopoietic tissue (200-208)	0	4
No site specification (199)	1	1
	4	39

The malignant neoplasms are detailed in Table 20, the cell types of the neoplasms, as recorded on the death certificates, are summarized in Table 21.

Table 21

MORPHOLOGY OF NEOPLASMS

ICD Code 9th Ed.	Nomenclature	Deaths Ranch Hand	Deaths Comparison
M800	Neoplasms not otherwise specified (NOS)		
	Brain	0	1
	Bronchus and Lung	0	3
	Colon	0	1
	Intestinal Tract	0	1
M801-804	Epithelial neoplasms (NOS)		
	Bronchus and Lung	1	8
	Esophagus	0	1
	Kidney	1	1
	Nasopharynx	0	1
	Pancreas	0	2
	Unspecified site	1	1
M805-808	Papillary and Squamous Cell		
	Nasal Sinus	0	1
	Lip	0	1
	Tongue	0	1
	Tonsil	0	1
M814-838	Andenomas and Adenocarcinomas		
	Appendix	0	1
	Bronchus and Lung	0	2
	Colon	0	1
	Kidney	0	2
	Stomach	0	1
M872-879	Nevi and Melanomas		
	Skin (NOS)	0	1
	Mediastinal	1	0
M905	Mesothelioma		
	Bronchus and Lung	0	1
M938-948	Gliomas		
	Frontal Lobe	0	1
	Brain (NOS)	0	1
M959-963	Lymphomas NOS and Diffuse		
	Lymphomas (NOS)	0	1
M965-966	Hodgkins disease		
	Hodgkin's (NOS)	0	2
M986	Myeloid Leukemias		
	Acute Myelocytic Leukemia	0	1
		4	39

Epithelial, papillary and adenomas account for 64% of the comparison neoplasms. Three Ranch Hand neoplasms arose from epithelial cells. There were no tumors in either group which were classified as soft tissue sarcoma.

Chapter IV

NONCAUSE SPECIFIC COMPARISONS WITH EXTERNAL POPULATIONS

1. Background and Motivation

It is important to know, not only how the Ranch Handers and their matched comparisons relate to each other, but also how they compare with general military and male United States populations. Pitfalls inherent in these comparisons are well known and are briefly reviewed below for specific comparisons with 1978 DoD period life tables for nondisability retired military officer and enlisted personnel (15) and the 1978 U.S. White Male Life Table (16). Although there are difficulties in the use of these comparisons, their use does provide an additional indicator of trends in mortality when viewed in the context of the total analytic process.

2. Adjustment Difficulties

Mortality rates in any military population are strongly dependent upon 1) calendar year of death, 2) military status (active duty, separated, retired), 3) selection and retention, and 4) branch of service. Adjustment for these effects was not made in these comparisons because published select Air Force life tables, by calendar year and by status, are not available. In addition, there is also a problem with the statistical method used, since the Gail and Ware (17) procedure assumes constant relative risk with respect to age; the selection effect has been shown to diminish sharply with time making this assumption untenable in these comparisons. The adjustment difficulties (1-4), and their likely consequences, are detailed below. These difficulties apply to all of the comparison groups, but these concerns have less effect on the comparisons of the Ranch Hand group to their matched cohort since these two groups are generally equivalent, relative to these key factors.

A. Adjustment for Calendar Year of Death

Due to the continuing decrease in overall mortality in the military (18) and in the United States (19), the referenced external age-specific rates are appropriate only for the calendar period of the referenced external life table, that is, 1977-79 for the 1978 period military table used in this analysis. The 1977-79 period rates would, for example, be too low for comparison with subjects dying in 1970 at the age of 40. These subjects would more properly be compared with the death rate for 40 year olds in a 1970 period life table or with a death rate for 40 year olds in a cohort military life table for subjects born in 1930. Calendar time is not taken into account in this analysis because period life tables covering the three decades from 1950 to 1980, for the the active duty, separated and retired Air Force subpopulations, are not currently available. This discrepancy is serious because the decline in death rates in the active duty Air Force during the period 1966 to 1980 has been very substantial (18).

B. Adjustment for Military Status (Active Duty, Separated, Retired).

The only published military life tables available at this writing are 1978 period tables for DoD nondisability retired officer and enlisted personnel (15) and a series of yearly abridged tables for the active duty Air Force, the first covering the period 1966-1968 and the last 1978-1980 (18). With these data limitations, adjustment for military status is not possible. It is clear, however, that there are substantial differences between active duty and retired death rates with the active duty rates being lower than retired rates (15).

C. Adjustment for Selection

Entry into the military carries with it an effect known as selection, a lengthening of life expectancy due to health prerequisites upon entry into select status and periodic health checks thereafter. This effect is well known to insurance actuaries who have observed that, in insured populations, the effect diminishes as time passes unless there are continued checks on the state of health of the insured persons (20). If selection is to be adjusted for in this analysis, it would be necessary to know Air Force death rates as a function of both age and of time elapsed since entry into the Air Force. It would also be necessary, therefore, to know enlistment and discharge or retirement dates for all study subjects. It is the lack of these data that makes this adjustment impossible at this time. The consequences of this lack of adjustment are not known at this writing.

D. Adjustment for Branch of Service

Age specific active duty Air Force death rates are substantially lower than the corresponding rates for other services (18). Nonservice specific death rates are therefore too high for appropriate comparison with these two study groups.

3. Comparisons with 1978 DoD Life Tables

In Tables 22 and 23, Ranch Hand officers and comparison group officers are contrasted to a 1978 DoD nondisability retired officer life table (15) and in Tables 24 and 25, Ranch Hand and comparison group enlisted personnel are compared with a 1978 DoD nondisability retired enlisted life table (15). In each table, the column labeled "At Risk" lists the number of subjects entering each five year age interval, the column labeled "Deaths" tabulates the numbers of deaths in the age intervals and the column labeled "Expected Deaths" gives the expected numbers of deaths in the age intervals if the study subjects had experienced the same death rates as those specified by the DoD table. The value of the test statistic (17) for testing the null hypothesis of equality is denoted by T; its two sided P-value is denoted by P. While each table summarizes the findings with five year age intervals for ease of presentation, one year age intervals were used for the computation of the statistic T. All comparisons are conditioned on survival to age 35, since the DoD tables begin at that age.

Table 22

RANCH HAND OFFICER VERSUS DOD NONDISABILITY RETIRED OFFICER LIFE TABLE
(T = -3.962, P < .001)

Age	At Risk	Deaths	Expected Deaths
35-39	456	2	4.183
40-44	366	1	4.244
45-49	288	1	4.578
50-54	173	1	3.099
55-59	57	1	2.043
60-64	30	2	.823
65-68	1	0	.076

Table 23

COMPARISON OFFICERS VERSUS DOD NONDISABILITY RETIRED OFFICER LIFE TABLE
(T = -2.402, P = .016)

Age	At Risk	Deaths	Expected Deaths
35-39	2264	12	20.837
40-44	1822	13	20.703
45-49	1365	24	21.920
50-54	842	12	15.901
55-59	308	9	10.265
60-64	145	4	4.377
65-68	19	0	.601

Table 24

ENLISTED RANCH HANDERS VERSUS DOD NONDISABILITY RETIRED ENLISTED LIFE TABLE
(T = -.239, P = .811)

Age	At Risk	Deaths	Expected Deaths
35-39	668	6	6.748
40-44	392	5	5.601
45-49	287	5	6.326
50-54	140	5	4.154
55-59	41	2	2.203
60-64	20	2	1.484
65-69	6	0	.576
70-71	1	1	.096

Table 25

ENLISTED COMPARISON SUBJECTS VERSUS DOD NONDISABILITY RETIRED ENLISTED LIFE TABLE

(T = -3.214, P = .001)

Age	At Risk	Deaths	Expected Deaths
35-39	3299	21	33.370
40-44	1945	20	27.681
45-49	1437	31	31.450
50-54	695	14	20.076
55-59	203	12	10.980
60-64	103	3	7.515
65-59	35	1	2.593
70-74	5	0	.646

These findings suggest that, if the effects discussed in section 2 are assumed to be negligible, Ranch Hand officers and comparison officers and comparison enlisted personnel are living longer than expected relative to their respective external populations. Enlisted Ranch Hand personnel are not different from DoD enlisted personnel. In the above DoD comparison there is a suggestion of interaction between officer-enlisted categories and Ranch Hand versus comparison group membership. If matching and time of death are ignored, the following table can be constructed. The term "rate" is as defined on page 8 of this report.

Table 26

DEATH AFTER 35 YEARS

	Ranch Hand			Comparison		
	Alive	Dead	Rate	Alive	Dead	Rate
Officer	448	8	.018	2190	74	.033
Enlisted	642	26	.039	3197	102	.031

Analysis using log-linear models shows a statistically significant interaction with $p \leq 0.05$. It appears that Ranch Hand officers have a lower mortality after age 35 than Ranch Hand enlisted or comparison officers or enlisted. However, the converse situation is noted considering mortality prior to age 35 and is significant with $p \leq 0.05$. The data for this analysis of mortality prior to age 35 is set out below.

Table 27

DEATHS BEFORE AGE 35 YEAR

	Ranch Hand			Comparison		
	Alive	Dead	Rate	Alive	Dead	Rate
Officer	456	7	.015	2264	14	.006
Enlisted	775	9	.011	3833	60	.015

These interactions will require further detailed analysis and evaluation, with specific consideration of medical covariables including risk taking, other life patterns and herbicide.

4. Comparisons with U.S. 1978 White Male Life Table

Non-Black Ranch Handers and non-Black comparisons are compared in this section with the population of White males, as represented by the 1978 U.S. White Male Life Table (16). Two serious and well known problems with the use of this table are the lack of adjustments for the calendar year and selection effects just described; when comparing occupational cohorts with national populations, the selection effect is known as the "healthy worker" effect. The pitfalls of these kinds of comparisons are well documented (21, 22, 23). In Tables 28 and 29, non-Black Ranch Handers and non-Black comparisons are compared, via the method of Gail and Ware (17), with the 1978 U.S. White Male Life Table (16). In Tables 30 through 33, non-Black officers and enlisted personnel in both study groups are compared with the same 1978 U.S. White Male Table.

Table 28

NON-BLACK RANCH HANDERS VERSUS 1978 U.S. WHITE MALE LIFE TABLE
(T=-4.588, P <.001)

Age	At Risk	Deaths	Expected Deaths
21-24	1171	2	9.003
25-29	1169	6	9.783
30-34	1163	7	9.396
35-39	1054	7	9.256
40-44	722	5	10.381
45-49	549	6	12.085
50-54	304	5	8.114
55-59	98	3	5.039
60-64	50	4	2.790
65-69	7	0	0.669
70-71	1	1	0.089
		46	76.605

Table 29

NON-BLACK COMPARISONS VERSUS THE 1978 U.S. WHITE MALE LIFE TABLE

(T = -11.230, P <.001)

Age	At Risk	Deaths	Expected Death
19-19	5816	1	10.325
20-24	5815	16	55.444
25-29	5799	27	48.592
30-34	5772	23	46.719
35-39	5245	31	46.124
40-44	3593	29	51.041
45-49	2675	50	58.810
50-54	1487	26	40.529
55-59	509	20	25.210
60-64	248	7	14.461
65-69	54	1	3.403
70-74	5	0	0.601
		231	354.540

Table 30

NON-BLACK RANCH HAND OFFICERS VERSUS 1978 U.S. WHITE MALE LIFE TABLE

(T = -4.575, P < .001)

Age	At Risk	Deaths	Expected Deaths
25-29	454	3	3.794
30-34	451	4	3.710
35-39	447	2	4.420
40-44	362	1	5.304
45-49	285	1	6.370
50-54	172	1	4.541
55-59	57	1	3.019
60-64	30	2	1.302
65-68	1	0	0.110
		15	32.570

Table 31

NON-BLACK COMPARISON OFFICERS VERSUS 1978 U.S. WHITE MALE LIFE TABLE
(T = -7.923, P < .001)

Age	At Risk	Deaths	Expected Deaths
25-29	2253	9	18.880
30-34	2244	5	18.530
35-39	2239	12	22.137
40-44	1801	13	25.841
45-49	1352	24	30.468
50-54	834	12	23.328
55-59	308	9	15.157
60-64	145	4	6.923
65-68	19	0	0.887
		88	162.151

Table 32

NON-BLACK RANCH HAND ENLISTED PERSONNEL VERSUS 1978 U.S. WHITE MALE LIFE TABLE
(T = -1.753, P = .080)

Age	At Risk	Deaths	Expected Deaths
21-24	717	2	5.510
25-29	715	3	5.988
30-34	712	3	5.686
35-39	607	5	4.836
40-44	360	4	5.077
45-49	264	5	5.716
50-54	132	4	3.573
55-59	41	2	2.020
60-64	20	2	1.488
65-69	6	0	0.588
70-71	1	1	0.089
		33	40.571

Table 33

NON-BLACK COMPARISON ENLISTED PERSONNEL VERSUS THE 1978 U.S. WHITE MALE LIFE TABLE
(T =-5.923, P < .001)

Age	At Risk	Deaths	Expected Death
19-19	3563	1	6.325
20-24	3562	16	33.938
25-29	3546	18	29.713
30-34	3528	18	28.189
35-39	3006	19	23.987
40-44	1792	16	25.200
45-49	1323	26	28.341
50-54	653	14	17.201
55-59	201	11	10.053
60-64	103	3	7.538
65-69	35	1	2.515
70-74	5	0	0.601
		143	213.601

Given the cautions just described, these findings suggest that the non-Black Ranch Handers and comparisons are living much longer than expected relative to the 1978 U.S. White Male Life Table. The ratios of the observed to the expected deaths described in Tables 28 and 29 reveal that the Ranch Hand and comparison subjects are experiencing death at only 60 to 65% of the rate of the U.S. white male population. The ratio is 0.461 for the subsette of Ranch Hand officers, 0.543 for comparison officers, 0.813 for enlisted Ranch Handers, and 0.669 for enlisted comparison subjects. The healthy worker effect is very likely a major contributor to the undoubtedly real differences between these study groups and the general population.

Chapter V

COMPARISONS WITH THE WEST POINT STUDY GROUP

1. Background and Motivation

The statistical and epidemiological literature is replete with warnings against the uncritical use of the SMR and related summary measures for comparing study groups with published vital statistics for national populations or subpopulations (5), (24), (25). Those cautions are based on the adjustment difficulties described in Chapter 4, Section 2, and departures from the assumption of constant relative risk across age intervals between the study group and the external population. These drawbacks can be avoided by not referencing an external standard at all, by using one of the study groups as the standard (13), or by using as an external standard a group of military personnel, born during approximately the same years, with the same mortality follow-up, as the Ranch Hand and comparison groups.

An external group of sufficient size for meaningful statistical comparisons is not available at this time. Mortality and year of birth data is available, however, on a small group of West Point graduates, the subjects of the West Point Follow-up Study. Although this group is too small for all but very crude statistical comparisons (1), it is the only known external data available at this time. The following comparisons are, therefore, primarily descriptive.

The West Point Study Group consists of 474 members of the West Point graduation class of 1956. These men have been followed up since then for morbidity and mortality. All members of that class were, or still are, officers in the U.S. Armed Forces. The purpose of the West Point study is to investigate the relationship between blood lipid levels and cardiovascular disease. Each study subject is physically examined biennially and blood samples are obtained for lipid and lipoprotein analyses at the USAF School of Aerospace Medicine (26).

2. Noncause Specific Comparisons of Ranch Hand and Comparison Subgroups with the West Point Study Group

For the purpose of these mortality comparisons, 15 of the 36 known West Point deaths occurring on or before 31 December 1982 were deleted, 9 of the 15 were killed in action, one was killed in 1959 in the line of duty and 5 were killed in automobile crashes prior to 1962. These deletions imitate the deletion of personnel killed in action from the Ranch Hand and comparison groups. Noncombat or accidental deaths prior to 1962 were deleted because death prior to 1962 would have precluded membership in the Ranch Hand or comparison groups. In addition, one West Pointer who is also a Ranch Hander, was deleted; that individual was alive on 31 December 1982.

A summary of the remaining 21 deaths among the 458 West Point subjects used in these analyses is given by year of birth in Table 34 and by age in Table 35. In Table 35 the column headed "censored" lists by age, the number of West Pointers alive on 31 December 1982.

Table 34

WEST POINT DEATHS BY YEAR OF BIRTH

Year of Birth	At Risk	Dead
1930	20	0
1931	59	2
1932	90	6
1933	136	8
1934	141	4
1935	12	1
	458	21

Table 35

WEST POINT DEATHS BY AGE

Age	At Risk	Censored	Dead
25-29	458	0	2
30-34	456	0	5
35-39	451	0	3
40-44	448	0	2
45-49	446	276	8
50-52	162	161	1
		437	21

In this analysis, non-Black Ranch Hand and comparison officers are compared, without regard to cause of death, with the West Point study group; all of the West Point subjects are non-Black. Non-Black Ranch Hand Officers were matched, one-to-one, by year of birth, to West Point subjects. Due to the relatively small number of Ranch Hand officers and the limited year of birth range imposed by the age of the Class of 1956, only 283 of the 458 West Point subjects received a matched Ranch Hander. Match sets with West Pointers having the same year of birth were then merged to create six match sets, corresponding to the six years of birth, 1930 through 35, of the West Pointers. To compare West Pointers with comparison officers, two non-Black comparison officers were matched to each West Pointer by year of birth. All West Pointers received two matched comparison individuals. Match sets with West Pointers having the same year of birth were merged, giving six match sets containing a total of 916 comparisons.

Logrank tests were carried out on these two matched data sets, and the results are summarized in Table 36. In these analyses, survival time is age at death. Censorship is due to survival to 31 December 1982. For those still alive on 31 December 1982, censoring time is age on that day.

Table 36

STUDY GROUP VERSUS WEST POINT GROUP
LOGRANK COMPARISONS WITH TWO-SIDED P-VALUES

Comparison	P-Value
Ranch Hand officer versus West Point	.218
Comparison officer versus West Point	.528

An SMR analysis, with the West Pointers being the standard, is summarized in Table 37.

Table 37

SMR COMPARISON OF NON-BLACK RANCH HAND AND COMPARISON
OFFICERS WITH THE WEST POINT STUDY GROUP

	(SMR = .530)			(SMR = .778)			(SMR = 1)		
Birth	Ranch Hand			Comparison			West Point		
Year	At Risk	Dead	Rate	At Risk	Dead	Rate	At Risk	Dead	Rate
25-31	95	2	.021	272	19	.070	79	2	.025
32	35	1	.029	164	7	.043	90	6	.067
33-34	60	1	.017	257	6	.023	277	12	.043
35-40	93	4	.043	223	5	.022	12	1	.083
		8			37			21	

The test for constant relative risk across year of birth strata gives a P-value of .229. Further, a likelihood ratio test suggests that these SMR's are not different (P = .392).

3. Cause Specific Comparisons

The cause specific death counts for the West Point Study Group are given in Table 38.

Table 38
WEST POINT MORTALITY BY CAUSE

Cause	Count
Accidents	6
Infectious disease	1
Malignant neoplasms	6
Circulatory	5
Digestive	1
Genitourinary	1
Ill defined	1
	21

Cause specific comparisons are carried out with three causes, cancer (malignant neoplasms), other diseases, and nondisease (accidents, suicides, homicides and ill-defined), with an adjustment for year of birth by stratification on year of birth. Relative risks are calculated using the method of Mantel and Haenszel (14). These results, based on the counts in Tables 39 and 40, are shown in Table 41.

Table 39

CAUSE SPECIFIC COMPARISONS
RANCH HAND OFFICERS VERSUS WEST POINT

		Ranch Hand		West Point	
Cause	Birth Year	At Risk	Dead	At Risk	Dead
Non-disease	1925-1933	166	1	305	5
	1934-1940	117	4	153	1
Cancer	1925-1930	72	0	20	0
	1931	23	0	59	1
	1932	35	0	90	3
	1933	36	0	136	1
	1934	24	0	141	1
	1935-1940	93	0	12	0
Other diseases	1925-1934	190	2	446	8
	1935-1940	93	1	12	1

Table 40

CAUSE SPECIFIC COMPARISON
COMPARISON OFFICERS VERSUS WEST POINT

Cause	Birth Year	Comparisons Number	Comparisons Dead	West Point Number	West Point Dead
Nondisease	1929-1931	272	11	79	1
	1932	164	2	90	2
	1933	148	1	136	2
	1934-1937	332	2	153	1
Cancer	1929-1931	272	2	79	1
	1932	164	2	90	3
	1933	148	1	136	1
	1934-1937	332	2	153	1
Other diseases	1929-1932	436	9	169	1
	1933	148	1	136	5
	1934	109	1	141	2
	1935-1937	223	3	12	1

Table 41

CAUSE SPECIFIC RELATIVE RISKS, P-VALUES
95% CONFIDENCE INTERVALS FOR LOG RELATIVE RISK

Cause	Comparison	RR	95% Conf Interval for Log Rel Risk	P-value	Power
Nondisease	RH vs WP	1.072	(-1.504 - 1.643)	.931	.051
	Comp vs WP	0.841	(-1.354 - 1.009)	.775	.059
Cancer	RH vs WP				
	Comp vs WP	0.690	(-1.634 - .891)	.564	.089
Other diseases	RH vs WP	0.474	(-3.540 - 2.047)	.600	.082
	Comp vs WP	0.779	(-2.367 - 1.867)	.817	.056
All causes	RH vs WP	0.539	(-2.191 - .954)	.441	.120
	Comp vs WP	0.728	(-1.940 - .306)	.702	.067

While the Ranch Hand versus West Point cancer comparison cannot be assessed using the Mantel-Haenszel procedure, the absence of Ranch Hand cancer deaths in this analysis is of interest. This finding is consistent with the apparent but nonsignificantly decreased Ranch Hand cancer mortality noted in the Ranch Hand versus matched comparison group analysis (Chapter III).

Chapter VI

STATISTICAL ASPECTS

1. Purpose

The purposes of this chapter are 1) to briefly describe each statistical procedure used in the preceding chapters 2) to state the underlying assumptions of each procedure and 3) discuss the validity of those assumptions in this study. The procedures used in this analysis were, survival curve estimates and confidence bands, linear rank tests, relative risk estimation and standardized mortality ratios. Points 1-3 are addressed for each procedure in Sections 2 through 5.

2. Survival Curve Estimation and Confidence Bands

The survival function of a homogeneous population, S(t), is defined as the probability of surviving t years. The problem is to estimate S(t) and make a confidence statement about that estimate based on randomly censored data. Randomly censored data occur in survival studies since analyses are usually carried out before all subjects have failed. In the present application, failure is defined as death and censorship occurs because most subjects are still living at the time of analysis. Other causes for censorship in this kind of epidemiological study are loss to follow-up or death from causes other than those of interest. Thus far in this study, there have been no subjects lost to follow-up, and all causes of death are of interest.

The survival function is estimated here by the product limit estimate K(t), also called the Kaplan-Meier estimate (6). This estimate is derived under the assumption that, in a life testing experiment with n subjects on test, exactly k subjects, with k less than n, are observed to fail; the other n-k remaining are observed only until they are censored. The subjects are assumed drawn randomly from a homogeneous population. Censorship is assumed to be independent of failure. The Kaplan-Meier estimator is asymptotically unbiased and reduces to one minus the empirical distribution function in the absence of censoring.

In the present application, the homogeneous populations are the Ranch Handers, the comparisons and various subgroups of these two groups. Death time, is taken as age at death measured to the nearest month; censoring time is age on 31 December 1982, measured to the nearest month. Survival time is age at death or age on 31 December 1982 for those subjects still living.

The process n[K(t)-S(t)] converges weakly to a zero mean Gaussian process, as n tends to infinity, under random censorship when the underlying survival function S(t) and the censoring distribution are continuous on a bounded interval (27). This convergence is the theoretical basis for the confidence band algorithm (7) used in Figures 2 and 3, Chapter III and Appendices VI.

The independence of death and censorship can be assumed to hold here since censorship (survival to December 31, 1982) is not being invoked on individuals because they appear to be at unusually high, or low, risk of death (28). Direct contact has been lost with two Ranch Handers and nine comparisons as described in Chapter II, but these are assumed to be alive, and hence censored at their age on 31 December 1982. The reason for this assumption is that the extensive death ascertainment system is believed to be thorough enough so that, had any of these subjects died, the death would have been detected. Hence, while contact has been lost, loss to follow-up for the purpose of mortality determination has not occurred (29). All other subjects still alive on 31 December 1982 are censored at their age on that date.

The validity of inferences based on the estimate K(t) and its associated confidence band depends on the sample size and the observed number of deaths. The sample sizes and numbers of deaths in every stratum used in these analyses exceed the minimum requirements for these procedures (7).

The survival curve estimates and confidence bands displayed in Figures 2 and 3 and Appendix VI are not adjusted for year of birth. To do so would have required stratification on year of birth, creating many small strata with associated sample size difficulties. Some year-of-birth adjusted plots in the larger occupational strata will be presented in the next report.

3. Linear Rank Procedures

The hypothesis of interest in this analysis is that the actual survival distributions of the Ranch Handers and their matched comparisons are identical. The procedures of choice for testing equality of the two unknown survival distributions based on the matched and censored data in this study are the censored data extensions of the exponential scores and Wilcoxon tests, due to Prentice (8). The first of these is widely known as the logrank test. The test statistics, T, are of the form given by equation 6-23 of (28), where the summands are calculated on match sets consisting of survival information on one Ranch Hander and his matched mortality comparisons. The statistic T, for either logrank or generalized Wilcoxon summands, is approximately standard normal under the null hypothesis (9).

The large sample normal approximation for T will hold when all distributions are continuous and all censoring times are mutually independent of each other and independent of death. These assumptions are well satisfied in this study since the censorship mechanism, survival to time of analysis, does not favor one group over the other.

In these procedures, the sampling unit is a match set, so that these tests are adjusted for all matching variables. Prior to calculation, match sets with Ranch Handers in the same race and job classification having the same year of birth are merged.

The logrank and extended Wilcoxon tests are locally most powerful when he logarithm of the survival times are distributed as extreme value or logistic random variates respectively. While the efficiency of these procedures peaks at these two underlying distributions, they have been shown to be robust against departures (8). These distributional assumptions, however, are not viewed as strictly valid in this study since there is good evidence in the literature that survival time due to certain cancers and other diseases is log normally distributed (30, 31, 32, 33). A linear rank procedure of the Prentice form, whose efficiency peaks under the lognormal distributional assumption, can be constructed (34), but this algorithm is not available at the present time; it will be included in the next analysis. The effect of this departure from the assumptions is considered mild. It should also be noted that these distributional assumptions cannot be checked since these match sets are small and the observations in the combined samples of all match sets cannot be assumed to have a common distribution. Therefore, reliance must be placed on historical data to determine which linear rank procedure to use. The logrank and Wilcoxon procedures are used here because they are powerful and widely accepted in epidemiology and statistics.

4. Relative Risk Estimation

Two relative risk estimators are used in this analysis, a generalization of the Ejigou-McHugh estimator for one to many matched data (12) and the Mantel-Haenszel estimator for stratified data (14). The Ejigou-McHugh estimate was chosen because it allows full adjustment for the one-to-many year-of-birth matching in this study, it is asymptotically as efficient as the maximum likelihood estimator and it is non-iterative. The Mantel-Haenszel estimate was chosen because of its ease of calculation, efficiency (35), and general acceptance. It's variance is estimated according to the advice of Anderson et al (36). Recent work suggests that the variance of the Mantel-Haenszel statistic might be better estimated by a jack-knife procedure (37); this newer method will be carried out in the next mortality report.

The Ejigou-McHugh estimator in its published form is suitable only for 1 to R matched designs in which the number, R, of controls matched to each case is the same for all cases. Since the number of controls matched to each Ranch Hander is not the same for all Ranch Handers, the Ejigou-McHugh estimate and its variance was extended to a one-to-many matched design in which the number of comparisons is allowed to vary from case to case. Since this extension is unpublished it is stated in Appendix V for reference.

The extended estimate and its variance reduces to the Ejigou-McHugh estimate and variance when all match sets contain an equal number of comparisons. It is asymptotically efficient and consistent and is non-iterative.

The Ejigou-McHugh estimate and the Mantel-Haenszel estimate are based on the assumption that relative risk is constant across levels of the matching variable. Some indication that this assumption holds in this study when the data is grouped, by stratifying on year of birth, is furnished by likelihood ratio testing; there is no evidence in this study to suggest that relative risk is not constant across levels of the matching variables when the event of interest is death from any cause. Therefore, the Ejigou-McHugh and Mantel-Haenszel estimates are appropriate for these data.

5. Indirect Standardization

With either an external or internal standard, the SMR is a good summary mortality index for comparing two or more populations, provided the product model, $P_{ij}=r_i p_j$, holds, where P_{ij} is the probability of death in stratum i of population j, r_i is a set of standard stratum specific rates and p_j characterizes the mortality of population j, $i=1,2, \ldots, I$, $j=1,2, \ldots, J$, (38, 13). If standard rates are known from some external source and if the product model holds, the best estimate of p_j is proportional to the SMR. If $J=2$, the product model holds, and if one of the two groups is used as the standard, the SMR estimates relative risk. In any case, any SMR summary of mortality data should be preceded by analytical and graphical tests of fit of the product model. Because one of the study groups was always used as the standard in these analyses, the test of fit of the product model was, equivalently, a test of constancy of relative risk across year of birth strata. The fit of the model was verified in each analysis. Further, a likelihood ratio test for equality of population was carried out as described by Gail (13). The results of both tests are summarized by their P-values in each application. The sample sizes in every application are large enough so that chi-square approximations hold; these analyses are, therefore, valid and appropriate.

The expected number of deaths in the SMR used in these analyses was calculated as $\sum n_{ij} P_i$, where n_{ij} is the number of subjects in the ith stratum of the jth population. The person-years SMR was not used here for two reasons. First, its validity as an estimator of relative risk is dependent upon the fit of the proportional hazards model for which an omnibus test is not currently available. Secondly, the person-years calculation is typically carried out from entry into follow-up (5); in this study, follow-up begins at first entry to Vietnam or Southeast Asia and these entry dates are being verified at this writing.

6. Comparing Observed Life Table Data with a Known Survival Curve

The procedure of Gail and Ware (17) is used in these analyses to compare Ranch Hand and comparison group survival data with published period life tables. The basic assumptions of this procedure are that death and censorship are independent competing risks and that the reference curve is a survival distribution for some external population. The test is of the form $\sum(o_j-e_j)/\sum(v_j)^{1/2}$, where o_j and e_j are observed and expected numbers of deaths in age interval j, and v_j is the variance of o_j-e_j. The statistic is not an omnibus goodness-of-fit test consistent against all alternatives to the null hypothesis that the observed sample comes from a known survival distribution. Rather, it has good power against proportional hazards alternatives or, more loosely, against alternatives for which the observed survival is better (or worse) in every interval than predicted by the known survival curve.

The independence of death and censorship assumption is well satisfied in these data, as discussed in Section 2 of this chapter. The life tables used in these analyses do not, however, represent the survival distribution of any population since they are period, not cohort, life tables. The appropriateness of this procedure is, therefore, dependent upon the extent to which these period life tables approximate the survival distribution of some relevant reference population. These period tables were used because the more appropriate cohort life tables were not available at the time of analysis.

Chapter VII

CONCLUSION

1. Introduction

The mortality analyses described in this report have not revealed any adverse death experience in the herbicide/dioxin exposed cohort. The results of the analyses, regardless of the source of the comparison data, were consistent: at this time, there is no indication that operation Ranch Hand personnel have experienced any increased mortality or any unusual patterns of death in time or by cause. They are not dying in increased numbers, at earlier ages, or by unexpected causes.

The fact that only a relatively small number of Ranch Hand deaths were available for analysis is reassuring in itself. However, the fact that adverse effects have not yet been detected does not imply that an effect will not become manifest at a future time or after covariate adjusted analyses. For this reason, further analyses are intended and mortality in the study population will be ascertained annually for the next 20 years.

A summary of the statistical techniques applied to each source of comparison data is presented in Table 42. It should be noted here that these analyses have been carried out without knowledge of covariate information, such as herbicide exposure, industrial chemical exposure, or other risk factors and that these analyses were carried out at a time when approximately 96% of Ranch Handers and their matched comparison subjects were still living. The data, therefore, must be viewed as preliminary to more definitive analyses, which will be performed over the next 20 years. Table 43 summarizes the results of the noncause specific analyses by source of the comparison data, and Table 44 presents the results of the cause specific analyses.

Table 42

SUMMARY OF STATISTICAL PROCEDURES USED IN ANALYSIS

Comparison Database	Internal Comparison Group	1978 U.S. White Males	1978 DoD Life Tables	West Point Class of 1956
Noncause Specific Analyses				
Logrank & Wilcoxon Procedures	+			+
Ejigou-McHugh Relative Risk	+			
Mantel-Haenszel Relative Risk	+			+
SMR/Breslow-Day Product Model	+			+
Gail-Ware Procedure		+	+	
Cause Specific Analyses				
Ejigou-McHugh Relative Risk	+			
Mantel-Haenszel Relative Risk	+			+

Procedure usage is indicated by a "+" symbol.

Table 43

SUMMARY OF NONCAUSE SPECIFIC MORTALITY ANALYSES BY SOURCE OF COMPARISON DATA

	Internal Comparison Group	1978 US White Males[1]	1978 DoD Life Tables[1]	West Point Class of 1956[2]
Ranch Hand Group	$RH = C$	$RH << US$		
	$RH_O = C_O$	$RH_O << US$	$RH_O << DoD_O$	$RH_O = WP_O$
	$RH_E = C_E$	$RH_E \leq US$	$RH_E = DoD_E$	
	$RH_F = C_F$			
	$RH_G = C_G$			
Comparison Group		$C <<< US$		
		$C_O << US$	$C_O < DoD_O$	$C_O = WP_O$
		$C_E < US$	$C_E < DoD_E$	
Internal Occupational Group Specific	$RH_O \leq RH_E$			
	$RH_F \leq RH_G$			
	$C_O < C_E$			
	$C_F = C_G$			

=	P value greater than .10	RH	Ranch Hand Group
≤	P value equal to or less than .10	C	Comparison Group
<	P value equal to or less than .05	O	Officers
<<	P value equal to or less than .01	E	Enlisted
<<<	P value equal to or less than .001	F	Flying
		G	Ground

[1] Validity of these comparisons is questionable (see Chapter 4)
[2] Statistical inference is limited by small sample size

Table 44

SUMMARY OF CAUSE SPECIFIC ANALYSES BY SOURCE OF COMPARISON DATA

RH Versus Internal Comparison	RH Versus West Point*
No significant difference in cause specific relative risks	No significant difference in cause specific relative risks

* Statistical inference is limited by small sample size

2. Internal Comparison Group

Based on these early results, there appears to be no significant difference between Ranch Handers and comparisons as regards mortality. This null finding holds for both cause specific and non-cause specific comparisons. One within group comparison did yield a significant difference, however. The non-Black comparison officers are living significantly longer than the non-Black comparison enlisted personnel. This may reflect the underlying health care and socioeconomic differences between these two groups. Non-Black Ranch Hand officers also appear to be living longer than non-Black Ranch Hand enlisted personnel, but this finding cannot be viewed as significant, with a P-value of .230 (Table 17). This lack of significance in the Ranch Hand analysis might be attributed to the smaller group sizes within the Ranch Hand cohort in contrast to the comparison cohort.

3. External Comparisons

As outlined in the study protocol, considerable effort was expended in the selection of the study comparison group. While the chosen comparison group appeared closest to the Ranch Hand cohort except for herbicide exposure, it seemed appropriate to also contrast the Ranch Hand mortality experience to that of additional comparison groups. Three additional comparison data sets were then selected: mortality data from the West Point Class of 1956, the DoD Non-Disability Retired Officer and Enlisted Life Tables for 1978, and the U.S. White Male Life Table, also for 1978. These data sets were chosen in a hierarchical fashion with the expectation that, in the absence of a herbicide effect, the Ranch Handers would have: 1) a mortality pattern comparable to the West Pointers, 2) a lower mortality than the DoD group due to the healthy worker effect, and 3) a still lower mortality than the U.S. male cohort due to healthy worker and military selection effects. These expectations were reassuringly fully realized with respect to overall mortality. Additionally, interesting officer-enlisted differentials emerged. As discussed below, these officer-enlisted differentials may have resulted from sample size effects or from covariable effects, potentially including herbicide exposure.

4. Power Considerations

The power limitations of this study, specifically regarding mortality from rare conditions, such as soft tissue sarcoma, were fully acknowledged and described in the protocol (Ref 1, page 67). For example, a fatal disease with an incidence of .001 would require an approximate risk of 4 for a power of 0.8.

Power calculations, while desirable for planning and study design, are also revealing at analysis. They are, however, sometimes difficult to carry out without further assumptions. The powers of the logrank and Wilcoxon tests and the likelihood ratio tests in the SMR analyses are not calculable at this time due to the lack of appropriate methodology. The powers of the tests for cause specific mortality were calculated at the estimated relative risk. The values were low because the estimates of relative risk were close to unity and/or the data were sparse.

The null findings in this report are unlikely to have been observed by chance had the true group differences been substantial. For example, if the true overall relative risk were in fact equal to 2, a crude calculation gives a probability of .0007 of observing a relative risk smaller than the observed .964 (Table 7). This probability is less than .001 if the true relative risk is 1.5. These findings are, therefore, very likely reflective of a near overall equivalence between Ranch Handers and their matched comparisons. Finally, these unadjusted findings do not preclude the possibility of the emergence of significant differences after adjustment for risk factors.

5. Consistency Patterns

When the analysis of each external comparison data base is considered separately, the restrictions inherent in each source limit the strength of the inferences which can be made. However, when the results of all internal and external comparison data bases are considered in context, some patterns of consistency emerge. While some of these patterns may not have firm statistical underpinnings, they still may provide epidemiologic clues to the dynamics of the mortality process.

The Ranch Hand officers exhibit a very consistent and predictable pattern across all analyses. As shown in Table 43, their mortality is nearly the same as that of their most equivalent comparison groups (the matched comparison group officers, and the West Point group). As the comparison groups become progressively less equivalent to the Ranch Hand group, the relative mortality of the Ranch Hand officers improves, presumably due to selection comparability (healthy worker effect, etc.). Their mortality is lower than that of their enlisted counterparts; however, this difference is not as striking as is the statistically significant comparable analysis between the matched comparison officers and the matched enlisted personnel.

Unfortunately, the cross-comparison trends for the enlisted Ranch Handers are not as clearcut. Their mortality is less, though not significantly different in a direct contrast with their matched comparisons. The enlisted comparison group had a highly significant underrepresentation of mortality against both the DoD and US life tables, whereas the Ranch Handers are equivalent to the DoD group and only marginally better than the 1978 US white males.

The consistent observation that the enlisted Ranch Handers appear to demonstrate less of a difference in relative mortality than do their matched comparisons is intriguing. This may reflect an actual increase in mortality due to herbicide exposure or some other factor, or it could be an artifact of small sample size created by the 1:5 matching or basic comparability problems as previously described. The inclusion of substantially more subjects in one group than another can have a profound effect on the significance level of a statistical technique. Nevertheless, these observations are of interest, and will continue to be subjected to detailed analysis throughout the course of the follow-up study. This trend is consistent with self-perception of herbicide exposure held by many of the Ranch Hand group. Covariate analyses will be conducted, the herbicide exposure index will be applied to these data, and the effects of interaction will be assessed to determine whether the Ranch Hand enlisted findings are real or artifactual.

The next mortality assessment will include analyses by person-year of follow-up, adjusted for age in an effort to better address the issue of latency. As the number of deaths in the study population increases with the passage of time, all of the statistical approaches outlined in the protocol (1) will be applied to the data.

Appendix I

RANCH HAND II PRINCIPAL INVESTIGATORS COINVESTIGATORS, CONTRIBUTORS, AND MANAGEMENT PERSONNEL

A. Principal Investigators

George D. Lathrop, MD, MPH, PhD, FACPM
Colonel, USAF,MC
Chief, Epidemiology Division

Patricia M. Moynahan, RN, MS
Colonel, USAF, NC
Chief, Occupational Epidemiology Section

Richard A. Albanese, MD, GM-15
Chief, Biomathematical Modeling Branch
Data Sciences Division

William H. Wolfe, MD, MPH, FACPM
Lt Colonel, USAF,MC
Chief, Epidemiology Services Branch

B. Coinvestigators

Joel E. Michalek, PhD, GS-13
Mathematical Statistician
Data Sciences Division

Richard C. McNee, MS, GM-13
Chief, Advanced Analysis Branch
Data Sciences Division

Alton J. Rahe, MS, GS-13
Mathematical Statistician
Data Sciences Division

Appendix I (Continued)

C. Contributors

William J. Besich, BS, GS-12
Computer Systems Analyst
Data Sciences Division

Vincent V. Elequin, BS, RRA, GS-11
Medical Record Librarian
Occupational Epidemiology Section

William E. Nixon, BS, GM-13
Computer Systems Analyst
Data Sciences Division

Thomas J. White, MA
Senior Subject Matter Specialist
Data Sciences Division

Alvin L. Young, BS, MS, PhD
Major, USAF
Special Assistant in Military Herbicides

D. Management Personnel

Project Director:

Roy L. DeHart, MD, MPH, MS, FACPM
Colonel, USAF, MC
Commander, USAF School of Aerospace Medicine

Project Resource Manager:

Melvin B. Dobbs
Colonel, USAF, BSC
Director, Systems Acquisition Research, Development and Acquisition
Aerospace Medical Division

Air Force HQ Systems Command Coordinator:

Ronald D. Burnett
Colonel, USAF, BSC
Command Bioenvironmental Engineer
Office of the Command Surgeon

Air Force Surgeon General Coordinator:

Robert A. Capell
Major, USAF, BSC
Assistant for Bioenvironmental Engineering
Office of the Surgeon General

Appendix II

SCIENCE PANEL

Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants.

Dr. G. W. Comstock
Johns Hopkins Research Center
Box 2067
Hagerstown MD 21740

Dr. John Doull
Professor
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City KA 66103

Dr. John A. Moore (Chair)
Deputy Director
National Toxicology Program
P.O. Box 12233
Research Triangle Park NC 27709

Dr. Richard Monson
Professor of Epidemiology
Harvard School of Public Health
677 Huntington Avenue
Boston MA 02115

Dr. Norton Nelson
Professor and Chairman
Department of Environmental Medicine
New York University
School of Medicine
New York NY 10016

Dr. Alan Poland
Associate Professor of Oncology
McCardle Laboratory
University of Wisconsin
Madison WI 53706

Dr. Irving Selikoff
Director, Environmental Sciences Laboratory
Mt Sinai School of Medicine
5th Avenue and 100th Street
New York NY 10029

Appendix III

MATCHING RESULTS IN THE MORTALITY POPULATION

The matching results are described here for the mortality population consisting of 1241 Ranch Hands, their 6171 matched mortality comparisons, and the six unmatched Ranch Hands. The matching procedure is described in the Protocol (Ref. 1, pages 23-26).

All study subjects were matched perfectly on job category. Three mismatches occurred on race because the recorded race designation for three study subjects were found to be incorrect at the LHA interview. These three subjects were comparisons, two were in the enlisted-other stratum (one was originally recorded as Black and was discovered to be non-Black, the other was originally recorded as non-Black and was discovered to be Black), and one was in the enlisted-flight engineer stratum (he was originally recorded as Black and was discovered to be non-Black).

Matching on date of birth was carried out by first expressing date of birth in months from 1 January 1900, to the nearest month; the result is termed month-of-birth. Six discrepancies occurred in matching on month-of-birth due to erroneous months-of-birth for one Ranch Hand and one comparison. These were discovered at the LHA interview. The Ranch Hand, in the non-Black enlisted-other stratum, was discovered to be 72 months older than was recorded prior to the matching. The comparison, in the non-Black officer-pilot stratum, was found to be 15 years younger than was originally recorded. The erroneous Ranch Hand month-of-birth put all five of his matched comparisons 12 months out of range since he was originally perfectly matched to all five mortality comparisons. The erroneous comparison month-of-birth put that comparison 119 months out of range. Given the very small number of mismatches on age and race relative to the number of subjects, their effect was assumed negligible.

The matching by month-of-birth, overall, and within each of the ten job and race categories within the mortality population is summarized in this Appendix. The column headed "Age Difference" lists absolute differences of months-of-birth of Ranch Hands and comparisons. The column headed "Number of Comparisons with RH younger (older)" gives, at each level of age difference, the number of comparisons within the level of age difference and older (younger) than the Ranch Hand to whom they are matched. The column headed "Total Count" gives the total numbers of comparisons having the absolute age differences with their matched Ranch Hand given in the first column; in "Total Per Cent", these counts are expressed as percentages of 6171. These are cumulated in the last two columns.

Appendix III

MATCH SUMMARY FOR THE MORTALITY POPULATION

		Number of Comparisons with RH		Total		Cumulative	
Strata	Age Difference	Younger	Older	Count	%	Total	%
Overall	0			4261	69.0	4261	69.0
	1-6	743	706	1449	23.5	5710	92.5
	7-12	77	102	179	2.9	5889	95.4
	13-18	40	36	76	1.2	5965	96.7
	19-24	22	22	44	0.7	6009	97.4
	25-30	12	19	31	0.5	6040	97.9
	31-36	16	14	30	0.5	6070	98.4
	37-42	10	19	29	0.5	6099	98.8
	43-48	9	13	22	0.4	6121	99.2
	49-54	13	7	20	0.3	6141	99.5
	55-60	17	7	24	0.4	6165	99.9
	72	0	5	5	0.1	6170	100.0
	179	0	1	1	0.0	6170	100.0
Officer-pilot Non-Black	0			961	55.2	961	55.2
	1-6	272	259	531	30.5	1492	85.8
	7-12	33	32	65	3.7	1557	89.5
	13-18	20	17	37	2.1	1594	91.6
	19-24	8	12	20	1.1	1614	92.8
	25-30	9	11	20	1.1	1634	93.9
	31-36	13	10	23	1.3	1657	95.2
	37-42	7	18	25	1.4	1682	96.7
	43-48	7	11	18	1.0	1700	97.7
	49-54	11	7	18	1.0	1718	98.7
	55-60	14	7	21	1.2	1739	99.9
	179	0	1	1	0.1	1740	100.0
Officer-Pilot Black	0			0	0.0	0	0.0
	1-6	3	0	3	23.1	3	23.1
	7-12	3	0	3	23.1	6	46.2
	31-36	0	1	1	7.7	7	53.9
	37-42	2	0	2	15.4	9	69.2
	43-48	1	0	1	7.7	10	76.9
	49-54	2	0	2	15.4	12	92.3
	55	1	0	1	7.7	13	100.0
Officer-Navigator Non-Black	0			240	61.5	240	61.5
	1-6	74	70	144	36.9	384	98.5
	7-12	0	6	6	1.5	390	100.0

Appendix III (Continued)
MATCH SUMMARY FOR THE MORTALITY POPULATION

Strata	Age Difference	Number of Comparisons with RH		Total		Cumulative	
		Younger	Older	Count	%	Total	%
Officer-Navigator Black	0			1	10.0	1	10.0
	1-6	0	1	1	10.0	2	20.0
	7-12	2	2	4	40.0	6	60.0
	13-18	0	1	1	10.0	7	70.0
	19-24	0	1	1	10.0	8	80.0
	25-30	0	1	1	10.0	9	90.0
	31-36	0	1	1	10.0	10	100.0
Officer-Other Non-Black	0			14	11.4	14	11.4
	1-6	38	57	95	77.2	109	88.6
	7-12	2	8	10	8.1	119	96.8
	13-18	1	1	2	1.6	121	98.4
	19-24	1	0	1	0.8	122	99.2
	25	0	1	1	0.8	123	100.0
Officer-Other Black	13-18	2	0	2	100.0	2	100.0
Enlisted-Flight Engineer Non-Black	0			516	55.2	516	55.2
	1-6	165	141	306	32.7	822	87.9
	7-12	29	34	63	6.7	885	94.7
	13-18	16	14	30	3.2	915	97.9
	19-24	0	7	7	0.7	922	98.6
	25-30	2	6	8	0.9	930	99.5
	31-36	2	1	3	0.3	933	99.8
	37-42	1	0	1	0.1	934	99.9
	46	1	0	1	0.1	935	100.0
Enlisted-Flight Engineer Black	0			10	13.3	10	13.3
	1-6	26	22	48	64.0	58	77.3
	7-12	7	5	12	16.0	70	93.3
	19-24	3	0	3	4.0	73	97.3
	55-58	2	0	2	2.7	75	100.0
Enlisted-Other Non-Black	0			2382	90.6	2382	90.6
	1-6	116	91	207	7.9	2589	98.5
	7-12	1	11	12	0.5	2601	99.0
	13-18	1	3	4	0.2	2605	99.1
	19-24	10	2	12	0.5	2617	99.6
	25-30	1	0	1	0.0	2618	99.6
	31-36	1	1	2	0.1	2620	99.7
	37-42	0	1	1	0.0	2621	99.7
	43-48	0	2	2	0.1	2623	99.8
	72	0	5	5	0.2	2628	100.0
Enlisted-Other Black	0			137	53.7	137	53.7
	1-6	49	65	114	44.7	251	98.4
	7-12	0	4	4	1.6	255	100.0

Appendix IV

YEAR OF BIRTH, OCCUPATIONAL AND RACE SPECIFIC MORTALITY

	Birth	Ranch Hand		Death	Comparison		Death
Job Category, Race	Year	At Risk	Dead	Rate	At Risk	Dead	Rate
Officer-Pilot, Non-Black	1915-19	8	3	.375	39	4	.103
	1920-24	31	0		155	13	.084
	1925-29	31	0		232	14	.060
	1930-34	113	3	.027	456	23	.050
	1935-39	66	3	.045	326	8	.025
	1940-44	60	1	.017	354	5	.014
	1945-49	40	2	.050	178	5	.028
	TOTAL	349	12	.034	1740	72	.041
Officer-Pilot, Black	1930-34	0	0		3	0	
	1935-39	1	0		4	0	
	1940-44	3	0		6	0	
	1945-49	2	0		0	0	
	TOTAL	6	0		13	0	
Officer-Navigator Non-Black	1925-29	9	0		47	3	.064
	1930-34	35	1	.029	163	7	.043
	1935-39	21	1	.048	105	3	.029
	1940-44	13	0		67	0	
	1945-49	2	0		8	0	
	TOTAL	80	2	.025	390	13	.033
Officer-Navigator Black	1930-34	1	0		6	0	
	1935-39	1	0		4	0	
	TOTAL	2	0		10	0	
Officer-Other, Non-Black	1910-14	1	0		2	0	
	1915-19	0	0		3	0	
	1920-24	1	0		6	0	
	1925-29	3	0		11	1	.091
	1930-34	2	0		12	1	.083
	1935-39	4	0		19	0	
	1940-44	13	1	.077	66	1	.015
	1945-49	1	0		4	0	
	TOTAL	25	1	.040	123	3	.024

Appendix IV (Continued)

	Birth	Ranch Hand		Death	Comparison		Death
Job Category, Race	Year	At Risk	Dead	Rate	At Risk	Dead	Rate
Officer-Other, Black	1940-44	1	0		2	0	
	TOTAL	1	0		2	0	
Enlisted-Flt Eng Non-Black	1915-19	1	1	1.000	6	2	.333
	1920-24	4	0		20	4	.200
	1925-29	12	0		61	3	.049
	1930-34	64	3	.047	304	15	.049
	1935-39	48	2	.042	243	10	.041
	1940-44	41	0		211	7	.033
	1945-49	19	0		90	5	.056
	TOTAL	189	6	.032	935	46	.049
Enlisted-Flt Eng Black	1925-29	1	0		10	1	.100
	1930-34	6	1	.167	34	5	.150
	1935-39	5	0		16	1	.063
	1940-44	3	1	.333	15	2	.133
	TOTAL	15	2	.133	75	9	.120
Enlisted-Other Non-Black	1905- 9	0	0		2	0	
	1910-14	4	2	.500	10	2	.200
	1915-19	8	0		48	5	.104
	1920-24	12	3	.250	60	7	.117
	1925-29	28	2	.071	140	18	.129
	1930-34	76	6	.079	376	14	.037
	1935-39	52	1	.019	263	8	.030
	1940-44	67	2	.030	340	7	.021
	1945-49	270	9	.033	1333	36	.027
	1950-54	11	0		56	0	
	TOTAL	528	25	.047	2628	97	.037
Enlisted-Other Black	1930-34	7	1	.143	35	2	.057
	1935-39	9	0		40	3	.075
	1940-44	7	0		35	1	.029
	1945-49	29	1	.034	145	4	.028
	TOTAL	52	2	.038	255	10	.039

Appendix V

THE EXTENDED EJIGOU-McHUGH RELATIVE RISK ESTIMATOR

Let R_k, $k=1,2, \ldots, K$, denote the distinct numbers of controls matched to the cases and let n_k denote the number of match sets with exactly R_k controls. A match set is defined as the case and his matched controls. Let $n=n_1+n_2+ \ldots +n_K$ denote the total number of match sets.

Define $Z_{k,i,T}$, $k=1,2, \ldots,K$, $i=0,1$, by

$Z_{k,0,T}$ = the number of match sets, among those having exactly R_k controls, in which the case is alive and exactly T of the R_k controls have died, $T=1,2, \ldots, R_k$

$Z_{k,1,T}$ = the number of match sets, among those having exactly R_k controls, in which the case has died and exactly T of the R_k controls have died, $T=0,1,2, \ldots, R_k-1$.

The extended estimate, ψ, is given by

$$\psi = \frac{\sum_{k=1}^{K} \sum_{T=1}^{R_k} Z_{k,0,T}Z_{k,1,T-1}/(Z_{k,0,T}+Z_{k,1,T-1})}{\sum_{k=1}^{K} \sum_{T=1}^{R_k} TZ^2_{k,0,T}/(R_k-T+1)(Z_{k,0,T}+Z_{k,1,T-1})}$$

and its variance is estimated by

$$\sigma^2 = \frac{\psi}{\sum_{k=1}^{K} \sum_{T=1}^{R_k} Z_{k,0,T}/[\psi+(R_k-T+1)/T]}.$$

Since K is finite, this estimate has the same distributional properties as the Ejigou-McHugh estimator; it is asymptotically efficient and unbiased. The underlying assumptions used in its derivation are that the disease under study is of low incidence and that relative risk is constant over the levels of the matching variables. The Ejigou-McHugh estimate and the above extension are equivalent in asymptotic efficiency to maximum likelihood estimation (12).

Appendix VI

Figure 4
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR POOLED RANCH HANDERS

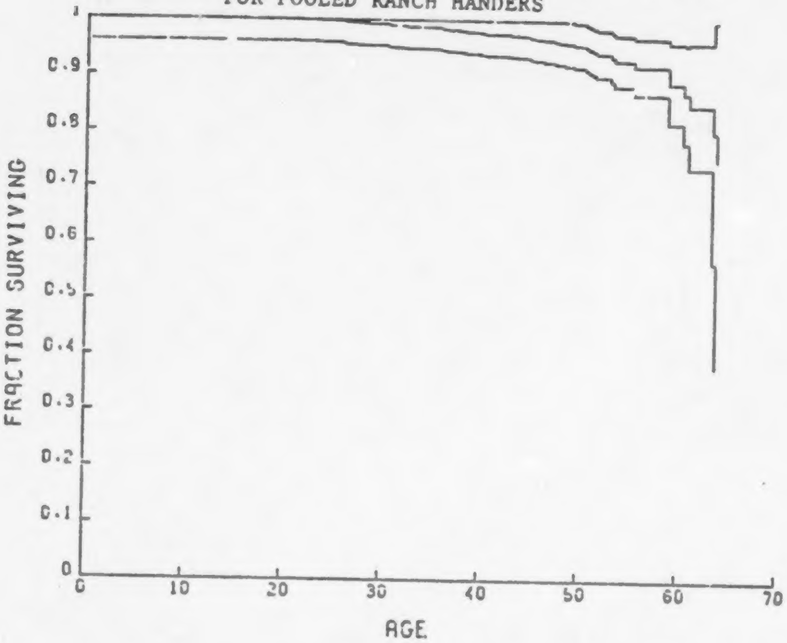


Figure 5
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR POOLED COMPARISONS

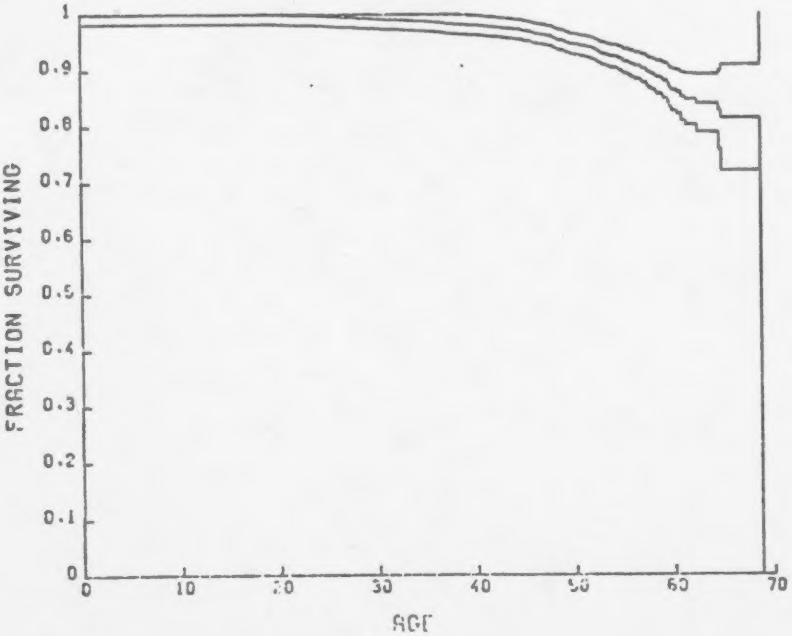


Figure 6
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR RANCH HAND OFFICERS

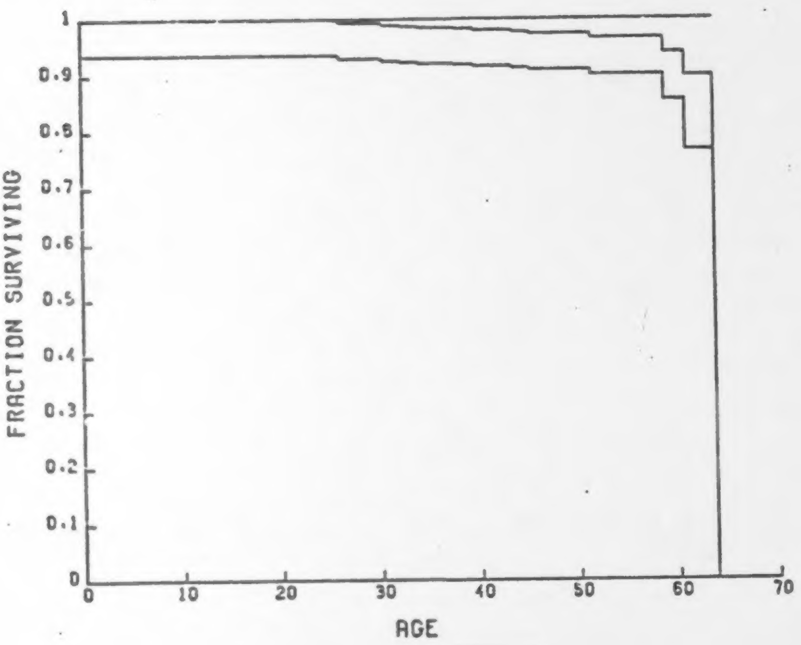


Figure 7
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR COMPARISON OFFICERS

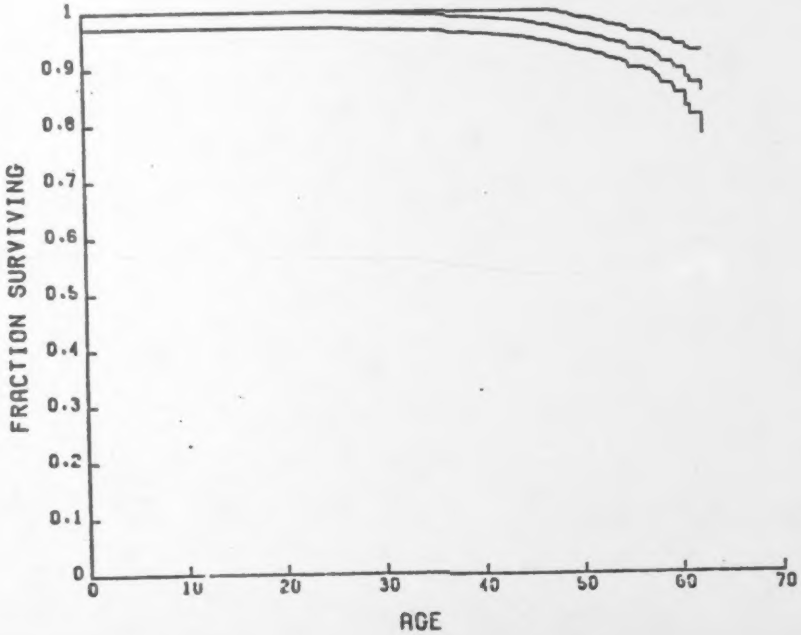


Figure 8
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR RANCH HAND ENLISTED PERSONNEL

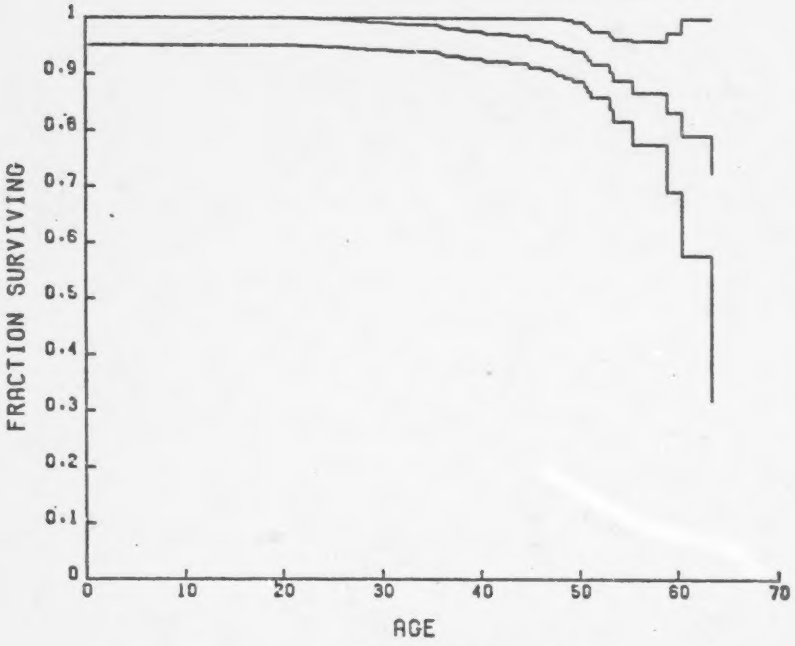


Figure 9
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR COMPARISON ENLISTED PERSONNEL

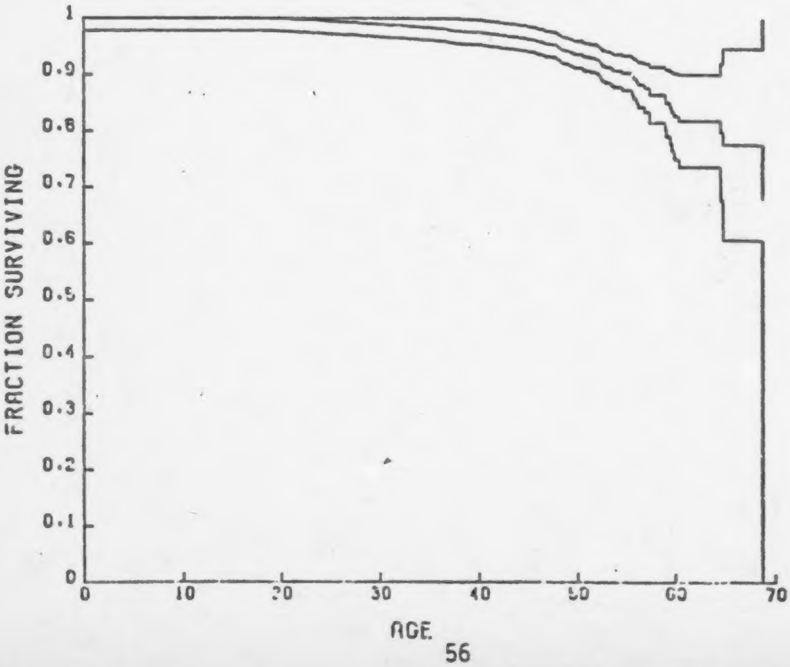


Figure 10
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR RANCH HAND FLYING PERSONNEL

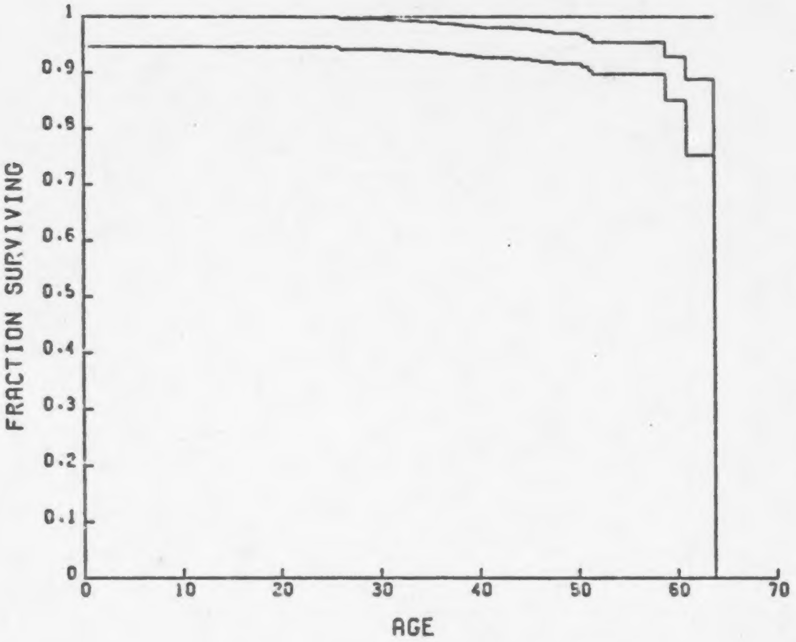


Figure 11
SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS
FOR COMPARISON FLYING PERSONNEL

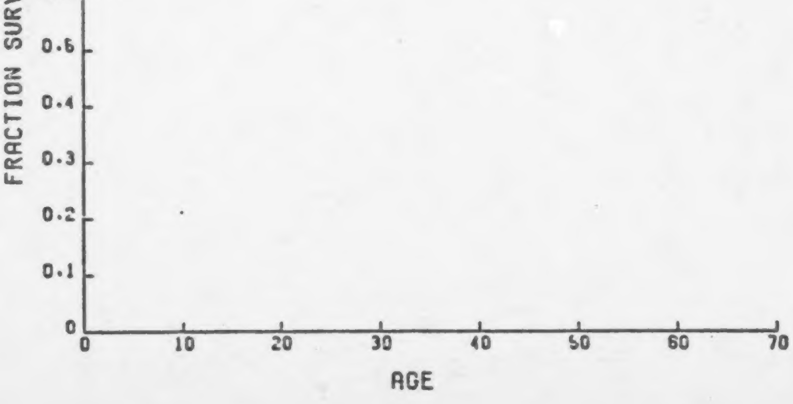


Figure 12

SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS FOR RANCH HAND GROUND PERSONNEL

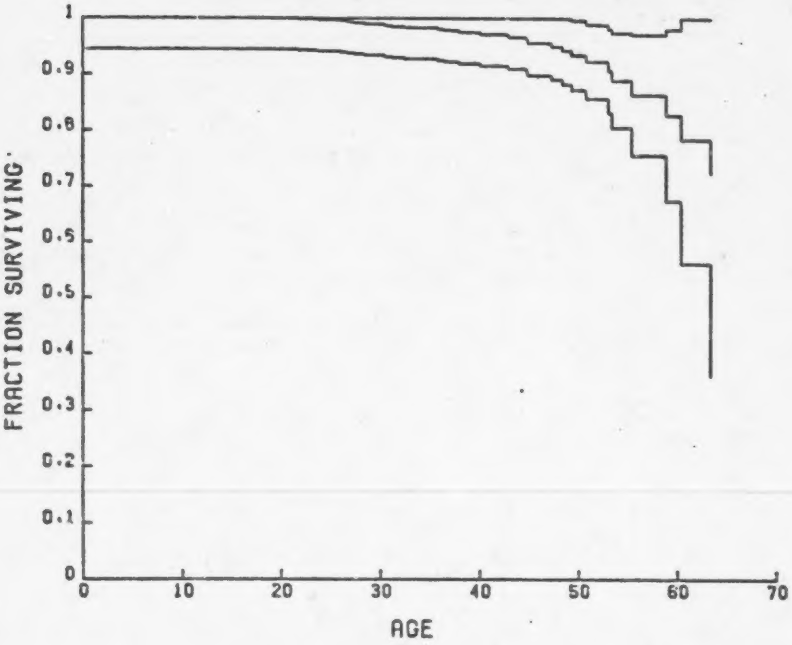
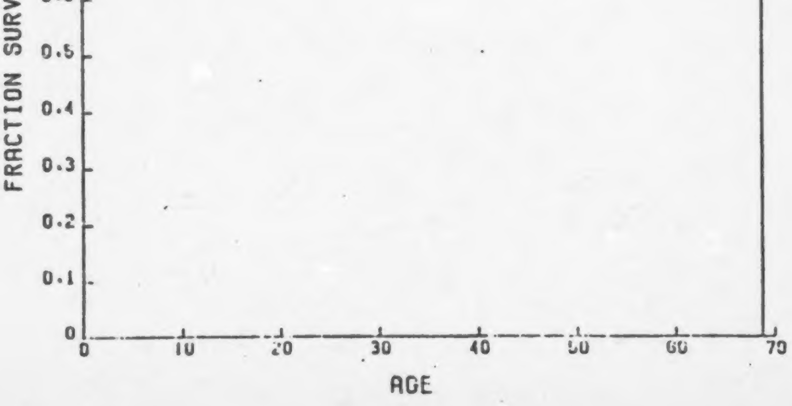


Figure 13

SURVIVAL CURVE ESTIMATE AND 95% CONFIDENCE BANDS FOR COMPARISON GROUND PERSONNEL



REFERENCES

1. Lathrop, G. D., Wolfe, W. H., Albanese, R.A. and Moynahan, P. M. Epidemiological investigation of health effects in Air Force personnel following exposure to herbicides: Study Protocol. SAM-TR-82-44, Dec 1982.

2. Honchar, P. A., and Halperin, W. E. 2,4,5-T, trichlorophenol, and soft tissue sarcoma. Lancet Jan 31:268-269 (1981).

3. Hardell, L., and Sandstrom, A. Case-control study: soft tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br. J. Cancer 39:711-717 (1979).

4. Eriksson, M., Hardell, L., Berg, N. O., Moller, T., and Axelson, O. Case-control study on malignant mesenchymol tumors of the soft tissue and exposure to chemical substances. Lakartidningen 76:3872-75 (1979).

5. Breslow, N. E., Lubin, J. H., Marek, P. and Langholz, B. Multiplicative models for cohort analysis. Journal of the American Statistical Association 78: 1-12 (1983).

6. Kaplan, E. L. and Meier, P. Nonparametric estimation from incomplete observation. J. Am. Stat. Assoc. 53: 457-481 (1958).

7. Hall, W. J. and Wellner, J. A. Confidence bands for a survival curve from censored data. Biometrika 67: 133-143 (1980).

8. Prentice, R. L. Linear rank tests with right censored data. Biometrika 65: 167-179, (1978).

9. Michalek, J. E. and Mihalko, D. Linear rank procedures for matched observations. SAM-TR-83-16 (In Press), May 1983.

10. Michalek, J. E. and Mihalko, D. Matched survival analysis (MSURV). SAM-TR-83-15 (In Press), May 1983.

11. Michalek, J. E. and Mihalko, D. Linear rank procedures for litter matched Data. Biometrics (to appear).

12. Ejigou, A. and McHugh, R. Relative risk estimation under multiple match-Biometrika 68: 85-91 (1981).

13. Gail, M. The analysis of heterogeneity for indirect standardized mortality ratios. Journal of the Royal Statistical Society, Series A 141: 224-234 (1978).

14. Mantel, N. and Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute 22: 719-748 (1959).

15. Valuation of the Military Retirement System FY 1980. Office of the Actuary, Defense Manpower Data Center, 300 North Washington Street, Alexandria, Virginia 22314.

16. Vital Statistics of the United States, 1978 Vol II - Section 5, Life Tables; U.S. Dept of Health and Human Services, DHHS Publication No (PHS) 81-1104; Hyattsville, Maryland:1980.

17. Gail, M. H. and Ware, J. H. Comparing observed life table data with a known survival curve in the presence of random censorship. Biometrics 35: 285-391 (1979).

18. Annual Report, 1966-1981, Servicemen's Group Life Insurance Program, Insurance Service, Department of Veterans Benefits, Veterans Administration.

19. Cohort Mortality and Survivorship: United States Death-Registration States, 1900-1968. Public Health Service. DHEW Publication No (HSM) 73-1400.

20. Elandt-Johnson, R.C. and Johnson, M.L. Survival Models and Analysis New York: John Wiley, 1980.

21. McMichael, A. J., Standardized Mortality Ratios and the "Healthy Worker Effect": Scratching Beneath the Surface. J. of Occupational Medicine, Vol 18, No. 3, March 1976.

22. Tabershaw, I. R., Special Communications, "What Do We Expect from an Occupational Cohort?", J. of Occupational Medicine, Vol 17, No. 2, February 1975.

23. Enterline, P. E. ; Pitfalls in Epidemiological Research; J. of Occupational Medicine, Vol 18, No. 3, March 1976

24. Gaffey, W. R. A critique of the standardized mortality ratio. Journal of Occupational Medicine 18: 157-160 (1976).

25. Wong, O. Further criticisms of epidemiological methods in occuptions studies. Journal of Occupational Medicine 19: 220-222.

26. Clark, D., Allen, M. and Wilson, F. Longitudinal study of serum lipids-twelve year report. American Journal of Nutrition 20: 743-752 (1967).

27. Breslow, N. and Crowley, J. A large sample study of the life table and product limit estimates under random censorship. The Annals of Statistics 2: 437-453 (1974).

28. Kalbfleisch, J. D. and Prentice, R. L. The Statistical Analysis of Failure Time Data. New York: John Wiley, 1980.

29. Monson, R. R. Occupational Epidemiology, CRC Press, Inc., Boca Raton FL (1980).

30. Feinleib, M. A method of analyzing log-normally distributed survival data with incomplete follow up. Journal of the American Statistical cal Association 55: 534-535 (1960).

31. Feinleib, M. and McMahon, B. Variation in the duration of survival of patients with chronic leukemias. Blood 15: 332-349 (1960).

32. Nice, C. M. and Stenstrom, K. W. Irradiation therapy in Hodgkins disease. Radiology 62: 641-652 (1954).

33. Osgood, E. E. Methods for analyzing survival data, illustrated by Hodgkin's disease. American Journal of Medicine 24: 40-47 (1958).

34. Mehrotra, K. G., Michalek, J. E., Mihalko, D. and White, T. Score computation for linear rank procedures. Journal of Statistical Computation and Simulation 16: 201-211 (1982).

35. Breslow, N. Odds ratio estimators when the data are sparse. Biometrika 68: 73-84 (1981).

36. Anderson, S., Auquier, A., Hauck, W., Oakes, D., Vandaele, W., and Weisberg, H. Statistical methods for comparative studies, techniques for bias reduction. New York: John Wiley, 1980.

37. Breslow, N. E. and Liang, K. Y. The variance of the Mantel-Haenszel estimator. Biometrics 38:943-952 (1982).

38. Breslow, N. E. and Day, N. W. Indirect standardization and multiplicative models for rates, with reference to the age adjustment of cancer cidence and relative frequency data. Journal of Chronic Diseases 28: 289-303 (1975).

WRITTEN COMMITTEE QUESTIONS AND THEIR RESPONSE

Question 1. The findings of the Ranch Hand study revealed that enlisted personnel had a higher mortality rate than officers. How many Ranch Hand personnel in the study were flight crew personnel?

Answer: 641

Question 2. How many were ground support personnel?

Answer: 606

Question 3. How many of the flight crew personnel were officers?

Answer: 437

Question 4. What was the average duration of a Ranch Hand mission?

Answer: An average Ranch Hand mission lasted approximately 1.4 hours. The actual spraying of defoliants during these missions took 4–10 minutes, depending on the amount to be sprayed.

Question 5. What was the average length of tour of duty for Ranch Hand personnel?

Answer: In July 1964, a permanent Ranch Hand unit was activated in the Republic of Vietnam. Permanent personnel gradually replaced temporary personnel so that by the end of 1964, Ranch Hand was a permanent unit. Beginning with the permanent unit, the average length of tour was 12 months. Prior to July 1964, all Ranch Hand personnel were assigned in a temporary duty (TDY) status. The TDY tours averaged between 120–180 days for each Ranch Hander. Many of the Ranch Handers served more than one tour.

Question 6. Were all Ranch Hand personnel, including pilots and support personnel, assigned in Vietnam for a full 12 month tour of duty?

Answer: No. In July 1964, a permanent Ranch Hand unit was activated in the Republic of Vietnam. Permanent personnel gradually replaced temporary personnel so that by the end of 1964, Ranch Hand was a permanent unit. Beginning with the permanent unit, the average length of tour was 12 months. Prior to July 1964, all Ranch Hand personnel were assigned in a temporary duty (TDY) status. The TDY tours averaged between 120–180 days for each Ranch Hander. Many of the Ranch Handers served more than one tour.

Question 7. How many were assigned on rotation, or temporary duty—3 or 6 months?

Answer: Approximately 100 individuals were on a temporary duty status, the remainder were on permanent status; however, many served more than one tour of duty.

STATEMENT OF SAMMY LEE DAVIS
TO THE COMMITTEE ON VETERANS' AFFAIRS
U.S. HOUSE OF REPRESENTIVES, JULY 12, 1983

Gentlemen;

I am a country boy, and I was raised with a country boy's love for this nation and belief in what my government was doing. In 1966, I joined hundreds of thousands of young men who voluntarily enlisted in the armed forces because we were convinced America needed us to serve her, a step I would take again today without hesitation. On a November night in 1967, good fortune and determination delivered me from a most difficult set of circumstances and I was awarded the honor I humbly display today. Throughout the darkest night of my life, although there was no one immediately present at my side, I never for a moment doubted that America herself was standing next to me. I come here today to join you, once again standing alongside America, seeking to serve her best interests.

Upon my discharge from the service in 1969, the state of my health began to lead me on a journey that, in many respects, is not unlike my travels through a jungle on the other side of the world. I have walked miles of hospital corridors while in pain; seeking the answers, fearing the worst, but pressing on because I believed it to be my duty to my family and myself. While there was always another prescription, additional speculation and what I believe to be a sincere effort to find the cause, the supreme question - why - could never be answered. And the pain could never be stopped.

The pain continues, the fear of the worst grows. But in March of this year, I broke through the jungle into the light. One man, Dr. Bertram Carnow, was able to tell me what both he and I believe to be the cause of my suffering. While I have suspected for some time that Agent Orange, and the dioxin contained in it, may be responsible for the illnesses that have cost me nearly four years of time off in the nine years of my employment with the company I must now retire from, it was only Dr. Carnow who has been able to confirm that. I assure you that it is only my faith in Dr. Carnow, his confidence in his tests and ultimate diagnosis, not my suspicions, that are responsible for my belief in his opinion.

The diagnosis has given me both fright and relief. I know, and the doctor has confirmed, that I am not a healthy man. From my conversations with Dr. Carnow, I know that without the same good fortune that delivered me from the jungle 14 years ago, I may be called away very soon. I am 36 years old, gentlemen, and that terrifies me. But at the very least, the darkness of uncertainy has passed and I can rest with the fact that I know what to expect.

I did not travel the miles from West York, Illinois yo the Capitol to accuse anyone or any organization of any wrongdoing, indifference or malpractice of medicine. None the less, certain questions exist in my mind and the minds of thousands of other Vietnam veterans. What can one doctor in Chicago do that the largest health care delivery system in the world cannot? What can one man examine, understand and diagnose that the largest health care delivery system in the world cannot? Can men who may not have years to wait for the completion of research be asked to stand by while there is a doctor who can answer their questions today? I submit, gentlemen, that we have a right to know, just as we did in Vietnam, why we may have to die.

I have come here today to lend what support I can to Congressman Daschle's legislation for two reasons. First, it will allow the Veterans' Administration to give immediate benefits to the men who are suffering, who cannot work and who can no longer feel the pride of making a contribution that they felt while they were in Vietnam. Secondly, in the long run, approval of this legislation by the Congress will be a definitive signal to the nation and the rest of the world that a problem does exist from exposure to Agent Orange and that the greatest deliberative body the world has ever known wants answers to the problem. Beyond compensation, it will be a call for intensified research in both the public and private sectors into the damage this chemical has caused, the means to halt the damage and the way to a cure.

A great American hero, Lou Gehrig of the New York Yankees, once told a capacity crowd in a baseball stadium that, in spite of the fact that he knew he was dying, he considered himself the luckiest man alive. Although I do not consider myself a hero, in light of the fact that Mr. Gehrig is no longer with us, I feel that I am now the luckiest man alive. I have been blessed with a beautiful, loving wife who, in turn, has blessed me with three beautiful, healthy children. I have also been given the rarest of opportunities in serving the greatest nation on the planet in a way few men are allowed to. I pray only that my family be allowed to grow and prosper in the same manner I was, and am left speechless when I consider the bounty that has befallen me.

Another man who was a hero, although perhaps only to me and the rest of his family, was my grandfather. When I returned from Vietnam, he gave me a newspaper clipping that I still carry with me today. The clipping is a rendition of the last two stanzas of Lt. John McCrae's poem "In Flanders' Fields". I would like to share some of the poem with the committee, because he told me it explained what serving in a war really meant.

"To you from failing hands we throw
the torch; be it yours to hold high.
If ye break faith with us who die
We shall not sleep, though poppies grow
In Flanders' fields."

I am an American, gentlemen, and therefore too proud and too bull-headed to beg you. But I humbly request that you do not break faith with those of us who answered the call that came from this very building. Think of the legacy you will leave for the next army you may have to raise to stand under our flag should you turn your backs on us. I can only ask you to do what is right.

Thank you for allowing me the honor of being here today.

MEDICAL REPORT ON SAMMY DAVIS
1047-010505
EXAMINED ON MARCH 11, 1983

HISTORY

CHIEF COMPLAINTS

This 36-year-old white male, Congressional Medal of Honor winner, complains of:

1. Dizziness associated with blurred vision.
2. Tingling of the hands and feet.
3. Nausea.
4. Tenderness, right upper abdomen.
5. Stiffness of all joints.
6. Muscle spasms involving the backs, legs and arms.
7. Heart pains, pains in the left chest going into the left arm.
8. Progressive weakness.
9. Diarrhea and constipation.

PRESENT ILLNESS

This man dates his symptoms essentially back 15 years to his service in Viet Nam during 1967 and 1968.

1. Dizziness and blurred vision - These symptoms have been worsening over the last three years, but have been present since his combat experience in Viet Nam. He gets momentary spells associated with blurred vision, when he might lose his balance. He has fallen on occasion. In the winter of 1982 he fell at work during one of these spells hitting his head on the door and hurt his neck. He was treated by a chiropractor for a number of weeks because of stiff neck. He was not unconscious. He has had the spells even as most recently as this morning just when walking along. There was no correlation with activity or position, although he can't recall getting spells while lying in bed asleep.

2. Tingling in feet - All the time he feels as though his hands and feet are asleep or tingling and especially of his toes and the 4th and 5th fingers of each hand. His hands feel like gloves.

3. Nausea - He has been troubled with nausea during the day for 15 years, often feels like he is going to throw up. The last time he threw up was in February when he vomited a meal of mashed potatoes and gravy about three hours after he had eaten it. He does not recall the appearance of the vomitus. He was worked up

for ulcers and had gastrointestinal series with no ulcers being found. He gets only slight relief from antacids such as Bromo Seltzer. His weight has fluctuated from 220 to 275 lbs. He now weighs 232 lbs.

4. Diarrhea and constipation - He has suffered from spells alternating diarrhea and constipation for the last 15 years. Prior to his military service he never had any difficulty with his digestion. The last two or three days he has had diarrhea consisting of some watery stools. Today he had two watery stools in the early morning, but none since. The diarrhea and constipation are not associated with nausea.

5. Tenderness, right abdomen - He has had this complaint for 15 years and work-up at various hospitals has not shown the cause. Is not connected with his constipation or nausea. One doctor told him his liver was enlarged and another told him he had an irritable bowel or colitis.

6. Stiffness in joints - He was troubled with stiffness in all joints; shoulders, elbows, knees, hips also dating back to his Viet Nam service. In 1969 he had a severe attack of stiffness in his elbows while still in the service. Could not even lift a coffee cup at that time. He was told that he has gouty arthritis and was placed on Zyloprim. Nobody else in his family has gout. He never had any actual swelling or redness of the joints. In 1976 he had a severe injury to the left knee with many ligaments being torn when a recreational vehicle turned over. He had two operations in 1976 and 1977 with a good result in his opinion.

7. Muscle spasms - He has been getting spasms all up and down his back and in his thighs for 15 years. He suffered severe injuries in combat while in Viet Nam with pentration of fletches into his left kidney, back and vertebra and at the same time a bullet wound to the soft tissue of the posterior right thigh and was also run over by a dislodged cannon. Apparently, there were no fractures, however, he was on crutches for many months. He did return to combat. During the same time he had a severe febrile illness and he was told that he had malaria. He also had kidney

8. Heart pains - Mr. Davis gets sharp pains in his left anterior chest over the pectoralis area which go into his left arm, leaving his left arm numb. These are not associated with any specific activity.

9. Weakness - He has been troubled in recent years with progressive weakness so that he can no longer grip things and also he tires very easily after a few hours and it takes him two or three days to recover his strength. He has been undergoing diagnostic tests and treatment at a VA Hospital in Minnesota and has not worked since December. Medications which he is now on are Amitriptyline, Zomax which he takes rarely, Darvon-N 100 of which he takes 4-6 a day, Zyloprim which he takes irregularly. He states that he is not using the Amitriptyline regularly because it makes him too drowsy and does not seem to be of benefit.

PAST HISTORY

He had pneumonia as a child, being hospitalized at the age of 3 or 4 years and apparently had frequent respiratory problems as a very small child. He was then in good health aside from such illnesses as measles and chickenpox. In high school he was very active participating in many teams and being very athletic. He played football, soccer among other activities.

While in Viet Nam in addition to the above noted injury he suffered a white phosphorus burn to the right hand when trying to light a flare. There are no residual symptoms from that. Also as noted above, he suffered severe injury to the left knee when a recreational vehicle rolled over in 1976. This was in a recreational activity. He has been hospitalized numerous times at various Veteran's Administration hospitals for diagnostic tests because of his multiple symptoms. He has had EMG's and EKG's all of which he believes have been normal. He had a stress test and was told that he had a very healthy heart. He had knee surgery in 1976 and 1977 as noted above. He has had several upper and lower gastrointestinal series with no abnormalities being noted. He is even now under a course of treatment at a VA hospital in Minnesota which specializes in work-up and treatment of "Agent Orange" victims. He does not feel he has benefited much. He is undergoing analysis for long standing psychiatric disturbances since his war injuries and again he feels that he does not benefit from these. He takes very little of the Amitriptyline because it aggravates his dizziness.

MEDICAL REPORT ON SAMMY DAVIS
1047-010505
EXAMINED ON MARCH 11, 1983

FAMILY HISTORY

He has been married 14 years. His wife is in good health aside from some asthma. He has three children; 4, 7 11 and one child also has some allergies. His wife had a tubal ligation after the birth of the youngest child. One brother was killed in an accident many years ago. He has three other siblings who are in good health. His father died of lung cancer at the age of 57. He was a construction worker. His mother is alive and well, but has lupus. One aunt has diabetes.

SOCIAL HISTORY

He smokes a pack a day and has done so since the age of 18. He drinks alcohol on rare social occasions. Activities that he likes are fishing, hunting and trapping. He did some fishing last summer, but has not felt like doing his usual recreation because of progressive weakness. He is active in numerous veteran's organizations and travels about the midwest making speeches to patriotic societies.

OCCUPATIONAL AND ENVIRONMENTAL HISTORY

Mr. Davis was born in Ohio, but has lived in Illinois for most of his life except for his service time. He finished high school in 1966 and then worked one summer in an oil field as a maintenance man on pump equipment, having contact with some crude oil. He then went into the service where he served in the artillery until 1969. His Viet Nam service was from 1967 to 1968. In addition to the injuries noted previously he gives the following history of exposure to defoliants. He does not know that they were necessarily Agent Orange. He participated in actions in the area south of Saigon in dense jungle and he states that the vegetation was always covered with an oily substance which was sprayed by helicopters. At the time, they were very pleased with this agent because it would turn jungle into "a golf course" in 24 hours and they frequently called for sprayings in order to facilitate their military actions. They used to bathe in rice paddy water which was coated with this oily substance. They had no way of cleaning themselves of course. He was directly sprayed on one occasion by a helicopter and lost his vision for three days. He was out of action during this time. He lost his vision because the spray went into his eyes. Also on several occasions, he mixed up formulations for this spray at the air field and did spill some of the substance on his clothes. No special precautions were taken in handling this material. He believes that it was mixed in fuel oil. He left the service in 1969 with a regular honorable discharge claiming no medical disabilities at that time. He worked for a year in a tool and die shop, but had to give up the job because of nerves. He was being progressively bothered with nightmares and daymares since his experiences in Viet Nam. He was then operating a pump press at a can factory, the only chemical he recalls being sorbital which was used as a lubricant. In 1974 he joined Central Illinois Power Service and has worked for them ever since. Started out as utility man, has now worked himself up to a pump operator. He operates a pumping system which circulates cooling water. Fuels used in his location are coal and oil. He has never had anything to do with atomic reactors. He states the temperature in his work place can often get tc 130 degrees and a protocol for rest time is followed when this happens. He has to operate large wheels which close valves in a definite sequence and has to climb stairs. He feels insecure in climbing the stairs, and as a matter of fact, in his 9 years with the power company has missed four years because of illness. He attended a course in 1976 for a year and a half to take an Associates Degree in the tool and dye business, but had to quit when he had his severe knee injury. He states that he does have some allergy to cutting oils, but he was able to do his tool and dye work with proper precautions and to avoid any skin problems.

REVIEW OF SYSTEMS

Head - He has headaches which in recent years have become worse and are associated with spells of fever when his wife has noted that his temperature goes up to 101.

Eyes - Feel like they are bulging and he takes Darvon which gives only partial relief.

Ears - On occasion he hears ringing in his ears.

Eyes - H wears glasses for reading.

Nose - He used to use nose bleeds, but not recently.

Throat - No symptoms.

Neck - See Present Illness.

Pulmonary - See Past History. No symptoms at present.

Cardiac - See Present Illness.

Gastrointestinal - See Present Illness.

MEDICAL REPORT ON SAMMY DAVIS
1047-010505
EXAMINED ON MARCH 11, 1983

Genitourinary - He has no gentourinary symptoms.

Neurologic - In addition to the neurologic syptoms described in the present illness, he is suffering from nightmare and daymares. These daymares which may come on at any time epsecially when he is in unfamiliar surroundings consisting of the onset of flashback and severe panic and may only last for a few seconds. He becomes very aggitated with these and if his wife is not around can be troublesome to the indivudals who are with him. His wife is able to calm him.

Reproductive - No problems.

Dermatologic - While in Viet Name he developed white blisters all over his skin and particularly on the scalp and he still gets a few of these during the summer. He also has had some scaly and weepy eruptions on the ears and some severe dandruff problem. He had some of these scaly lesions removed from his ears and was told by the medic that they were skin cancers, however he is not aware that there was laboratory confirmation of this diagnosis.

Musculoskeletal- See Present Illness. Mr. Davis describes muscle spasms in which he gets actual bunches or knots in his back and also tightness in his leg. These come on at any time even when he is lying in bed.

GSB/mj

MEDICAL REPORT ON SAMMY DAVIS
1047-010505
EXAMINED ON MARCH 11, 1983

Laboratory

Laboratory examination revealed abnormally increased triglyceride to 311, markedly depressed lipoproteins to 32 with Type 4, hyperprebeta lipoporteinemia. Polys are depressed to 45 and lymphs elevated to 50, Uric acid increased above normal. Peripheral nerve velocity conduction revealed both motor and sensory slowing of the right median nerve. ECG shows flat T-waves across most of the V leads and suggests a chronic coronary insufficiency with possible past occurrance of an antero lateral infarct. A sperm analysis reveals borderline value of 44.6 million. (60 to 150 million normal). Only 40% are active in 4 hours down from the normal 60% and 33% of the sperm are abnormal with 14% pathologic forms including cytoplasmic appendages and primitive forms.

Diagnosis

1. Chronic chemical intoxication from dioxin 2,4,5 T and 2,4 D (Agent Orange).
2. Probable damage to the central nervous system with petit mal type seizures, severe anxiety and mod.-severe depression
3. Peripheral neuropathy secondary to 1.
4. Lipid metabolism derangement secondary to chemical damage to the liver secondary to 1.
5. Conjunctivitis secondary to 1.
6. Possible damage to reproductive organs secondary to 1.
7. Hypertension secondary to 1.
8. Coronary insufficiency with possible myocardiopathy secondary to 1.
9. Polyarthralgia, secondary to 1.
10. Muscle spasm and muscle weakness secondary to 1.
11. Chronic gastritis and chronic enterocolitis possible secondary to 1.

MEDICAL REPORT ON SAMMY DAVIS
1047-010505
EXAMINED ON MARCH 11, 1983

Summary

This young man who was healthy before exposure, to dioxin was in Vietnam for a number of years. He has a history of extensive exposure to spray from airplanes which destroyed foliage, that is Agent Orange, and in addition was severely wounded, but apparently recovered from most of the wounds. He dates most of his symptoms since this exposure.

In regards to the central nervous system damage, he has severe dizzy spells with episodes suggesting petit mal seizures, nightmares and daymares, chronic anxiety attacks and is suffering from moderately severe depression which has been shown to occur in many of those exposed and affected by dioxin.

He has in addition very significant evidence of chronic disease of the peripheral nervous system with a history of tingling of hands and feet. On physical examination, he has abnormal decrease of sensation on both pin prick and touch. He also has evidence on peripheral nerve velocity conduction testing of abnormal slowing of motor and sensory fibers of the right median nerve. He also has evidence of damage to other organ systems known to be affected by dioxin and the other chemicals to which he was exposed, including a very significantly elevated triglyceride and a Type 4 hyper beta lipoproteinemia. In addition, his high density lipoproteins are markedly depressed placing him at very high risk to the development of heart disease. He has symptoms of pain in his left arm radiating out from his left chest and shows an abnormal Electrocardiogram. He has in addition an elevated blood pressure, and hypertension has been shown to occur in those exposed. He also has some abnormality of the reproductive system including some decrease in amount of sperm, the number active at 4 hours and the numbers of pathologic forms. In addition, he has a wide range of symptoms referrable to the gastrointestinal tract including nausea, vomiting, diarrhea and has little relief from medication. He has had multiple x-rays with no findings of an ulcer or other G.I. pathology.

The diseases that this young man is suffering from are those which are found in individuals exposed to these chemicals. He has in addition, a hyperurecemia but this has not been shown to be associated with dioxin. Cardiovascular abnormalities along with the gross abnormalities of lipid metabolism and the elevated blood pressure represent a serious problem. Additionally, he gives a history of having had multiple skin cancers, although none were found at the time of examination.

MEDICAL REPORT ON SAMMY DAVIS
1047-010505
EXAMINED ON MARCH 11, 1983

Prognosis

The prognosis in this case is very guarded. This man was heavily exposed 15 years ago and continues to have symptoms and findings of abnormalities of multiple organ systems. Additionally, the cardiovascular findings are of great concern. He also is at high risk to development of cancer because of his exposure and his youth.

Summary

This is a 36 year old white male who was heavily exposed to Agent Orange. He has a wide variety of symptoms, physical findings and laboratory findings compatible with chronic chemical toxicity as a result of absorption of chemicals into his body and subsequent damage to multiple organ systems. It is my opinion that these conditions are a result of and were caused by his exposure and absorption of dioxin and related chemical into his body.

Bertram W. Carnow, M.D.

STATEMENT

of the

AMERICAN MEDICAL ASSOCIATION

to the

Subcommittee on Compensation, Pension
and Insurance
Committee on Veterans' Affairs
U.S. House of Representatives

Presented by

John R. Beljan, M.D.

RE: Dioxin

July 12, 1983

Mr. Chairman and Members of the Subcommittee:

My name is John R. Beljan, M.D. I am Senior Vice-President of Wright State University in Dayton, Ohio. I am currently a member of the Council on Scientific Affairs of the American Medical Association. I served as chairman of the Association's Advisory Panel on Toxic Substances that prepared the AMA's 1981 report on "Agent Orange" and dioxin contamination. Accompanying me are Leonard D. Fenninger, M.D., AMA's Vice President for Medical Education and Scientific Policy, and Harry N. Peterson, Director of the Association's Division of Legislative Activities.

Mr. Chairman, we are pleased to accept your invitation to appear here today to discuss the AMA's view concerning the human health effects of exposure to the dioxin TCDD. This subject is particularilly important in light of the legislation cur ently before this Subcommittee.

H.R. 1961 would authorize disability payments to veterans who served in Southeast Asia during the Vietnam era who suffer from soft-tissue sarcomas, porphyria cutanea tarda and chloracne. Such payments would be allowed as "service connected" disabilities without establishing that the disease was contracted or aggravated in the line of duty. The bill would establish an entitlement to disability payments even if an individual never came into contact with "Agent Orange." The bill would also allow the Administrator of the Veterans Administration to establish by regulation other diseases "that medical research has shown may be due to exposure to herbicides, chemicals, medications, or environmental hazards or conditions."

In 1981, the AMA House of Delegates adopted a report entitled "The Health Effects of 'Agent Orange' and Polychlorinated Dioxin Contaminants." Copies of this report were submitted to the Subcommittee with our formal statement. This report was developed by the Association's Council on Scientific Affairs and was based on the investigation of its Select Panel on Toxic Substances of which I was Chairman. This report was initiated because of concern about the reported adverse health effects to humans from exposure to "Agent Orange" during the Viet Nam conflict. Medical complaints noted by veterans included weight loss, liver damage, recurrent skin rashes, deformed offspring, stillbirths, cancer, sterility, personality changes and other illnesses. The report, however, was not limited to studies involving exposure of U.S. forces to "Agent Orange" but included a review of all reported exposures during the last four decades. The dioxin TCDD was present in "Agent Orange" as a byproduct of its manufacture.

The AMA report on dioxin was an examination of the then-available current information on the effects of the substance on animals and human health. This study by our expert panel was a major undertaking given the very substantial amount of literature reporting experience with animal and human populations that has been generated over the last four decades. The report states, "TCDD by itself is extremely toxic; along with botulinus sacillus toxin and aflatoxin, it is one of the most lethal organic chemical compounds known to man." The report recognizes and describes the toxicity of TCDD pointing out the varying toxicity among different animal species and the relationship between toxicity and the amount and type of exposure and ingress to the body. This position, formulated in 1981, is still the policy of the AMA.

The report concludes that of the suggested adverse health effects on human beings attributed to dioxin exposure, there is conclusive evidence of a cause and effect relationship only with respect to chloracne. Chloracne is a not uncommon form of occupational dermatitis and may be caused by other chemical agents. It usually clears within several months of exposure, although severe chloracne may be persistent and has been known to last for as long as 15 years following cessation of exposure to the causal agent.

With respect to other suggested human health effects attributed to dioxin (TCDD), the Council on Scientific Affairs and its advisory panel concluded that there was insufficient published data subject to peer review to establish a relationship between dioxin exposure and the adverse health effect. The report reviews in detail the published scientific literature that supports these conclusions. I would note that the report of the Congressional Research Service of the Library of Congress entitled, "Dioxin: Environmental Impacts and Potential Human Health Effects," published June 6, 1983, surveys the body of scientific opinion and its conclusions. This survey is consonant with the 1981 AMA report.

In light of the foregoing, legislation should not go beyond chloracne associated with exposure to "Agent Orange" containing the dioxin TCDD.

Mr. Chairman, the AMA has a continuing obligation to promote the public health in matters such as this and to inform the profession and the public of the most current information. We note that this matter is not static and that new evidence will be reviewed as it becomes available. Therefore, we do not intend to let this important matter drop.

Action taken by our House of Delegates calls for an updating of our report on "Agent Orange" and dioxin this year along with an active program to provide the public the most accurate information available on dioxin. The new literature is scheduled to be reviewed by our expert panel next month. The findings are expected to be presented to the AMA Board of Trustees in October with consideration by the House of Delegates at its meeting in December. We will inform you of our conclusions.

Mr. Chairman, I will be happy to answer any questions the Subcommittee may have.

0945p

REPORTS OF COUNCIL ON SCIENTIFIC AFFAIRS

The following reports, A–G, were presented by William D. Dolan, M. D., Chairman:

A. HEALTH EFFECTS OF "AGENT ORANGE" AND DIOXIN CONTAMINANTS

(Reference Committee E, page 282)

HOUSE ACTION: ADOPTED

The American Medical Association's Council on Scientific Affairs, in response to a request from the Medical Student Section, has reviewed the medical evidence regarding the toxicity and long-term health effects of Agent Orange and its associated contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This Executive Summary, which was prepared by the Council on Scientific Affairs Advisory Panel on Toxic Substances,* summarizes the findings in its Technical Report on the subject, which is available on request.

BACKGROUND

During the latter stages of the United States' involvement in Vietnam, herbicidal mixtures of 2,4,-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), otherwise identified by the military as Agent Orange, were sprayed over certain areas of Vietnam for the express purpose of defoliating the jungle and destroying one of the enemy's means of concealment. Similar spray programs have been used in the United States as a means of forestry management. For the past thirty years, mixtures of 2,4-D and 2,4,5-T have been used extensively by the home-owner and farmer for ridding lawns and agricultural acreage of unwanted broadleaf vegetation. Large numbers of persons have been exposed to varying amounts of 2,4-D and/or 2,4,5-T, as well as the contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), in the normal course of employment.

Also over these years, there has been a number of industrial incidents wherein workers, as well as civilian populations, have been subjected to accidental exposure to these compounds. There are now pending a number of litigious actions and government regulatory responses that are based upon alleged adverse health effects from such exposures.

The most serious of these allegations by Vietnam veterans and persons who were involved in accidental industrial exposures assert that Agent Orange, or compounds of a like nature, may have caused malignant tumors, sterility, spontaneous abortions, birth defects, disfiguring skin diseases and other illnesses. In spite of the voluminous data on the biological effects of the phenoxy-type pesticides and the associated chlorinated dioxins, there is still very little substantive evidence for the many claims that have been made against these compounds. Data from experimental animals do indicate that TCDD is a toxic material; however, while suggestive, the animal data are not necessarily applicable to man. Still, a number of those exposures to TCDD of industrial and general populations that have occurred have been sufficiently well documented to offer some insight into the effect of TCDD on man.

Agent Orange, or Herbicide Orange, was a label given by the U. S. military forces to a 50:50 mixture of the n-butyl esters of 2,4-D and 2,4,5-T together with a minor amount (1%) of the free acid of 2,4,5-T and varying amounts of the contaminant TCDD. Agents Green, Pink and Purple also were used as defoliants by the military forces from 1962 through 1964; a time when very few American troops were committed to the field. Another formulation, Herbicide Orange II, was similar to Agent Orange except that the isooctyl ester of 2,4,5-T was substituted for the n-butyl ester of 2,4,5-T. In addition to Agent Orange, other spray defoliants used in Vietnam included Herbicide White, whose active ingredient was picloram (or the tri-isopropanolamine salt of 4-amino-3,5,6-trichloropicolinic acid). This substance is very persistent in the environment and highly carcinogenic in rats and mice. Lesser amounts of Herbicide Blue, which contained sodium cacodylate* (26%) and cacodylic acid (5%), were used. Though the long-term effects in humans of either or both of these compounds is uncertain, picloram and cacodylic acid should be considered along with the above agents that were encountered in Vietnam.

---

*John R. Beljan, M. D.; Nelson S. Irey, M. D.; Wendell W. Kilgore, Ph. D.; Kazuo Kimura, M. D., Ph. D.; Raymond R. Suskind, M. D.; Jaroslav J. Vostal, M. D., Ph. D.; R. H. Wheater, M. S., Secretary

TCDD may form as a by-product of the synthesis of 2,4,5-trichlorophenol (TCP), a precursor of 2,4,5-T, when 1,2,4,5-tetrachlorobenzene is subjected to alkaline hydrolysis at elevated temperature and pressure. If the reaction temperature is allowed to go above 180° C, the sodium-2-hydroethoxide (formed from the ethylene glycol solvent and caustic soda) decomposes exothermically and promotes the dimerization of sodium trichlorophenate to TCDD. The presence of TCDD as a contaminant of 2,4,5-trichlorophenol was discovered in 1957, when workmen involved in the manufacture of TCP developed chloracne.

About twenty years ago, commercially available 2,4,5-T contained anywhere from 1 to 70 ppm of TCDD. When the industry became aware of the contaminant's existence and toxicity, production operations were monitored and altered to reduce the level. Current manufacturing operations are able to control the amount of TCDD in commercial 2,4,5-T formulations to less than 0.01 ppm (with occasional batches as high as 0.05 ppm), a level believed to be non-hazardous to humans and other organisms. Data relating to an acceptable maximum level are presently under regulatory review by FIFRA (Federal Insecticide, Fungicide and Rodenticide Act); the recommended maximum concentration is now placed at 0.1 ppm.

Commercial formulations of 2,4,5-T and 2,4-D were used safely in agriculture for over thirty years with no recognizable evidence of carcinogenicity or birth defects in humans. Those adverse effects that did occur from massive doses of either pure 2,4-D or pure 2,4,5-T were manifested soon after the exposure, and the victims recovered with no signs of long-term damage. When the first symptoms were to present months or years after the last exposure to these compounds, it was evident another causal agent had to be responsible. That agent was later suspected to be TCDD. Though closely related chemically to 2,4,5-T, 2,4-D is not generally contaminated with TCDD.

BIOLOGICAL EFFECTS

Two of the more pronounced biological effects of some of the clorinated dioxins are their tendency to cause chloracne (especially, in the rabbit, nude mouse, monkey and man) and the accumulation of fluid (ascites) in the pericardium and peritoneal cavity of chicks.

Chloracne in man is typified by comedones in a malar distribution; the pre- and postauricular portions are often accompanied by hirsutism and sometimes by melanosis and a secondary inflammation. The disease was first described in 1899; its cause was discovered in 1918 to be due to contact with certain clorinated hydrocarbons. Chloracne has now become one of the more common forms of occupational dermatitis. Other acute toxic reactions to dioxin include liver and renal damage, porphyria cutanea tarda, hyperpigmentation, hirsutism, polyneuropathies (e.g., sensory impairments and weakness in lower extremities) and neurasthenic or depressive syndromes. Thus far, long-term effects, except for persistent chloracne, have not been seen.

Chloracne is not caused by 2,4,5-T and 2,4-D per se; if the condition occurs upon exposure to either or both of these compounds, it is most likely that the contaminant TCDD is responsible. Chloracne usually appears within 2 to 3 weeks after the first exposure. Mild chloracne clears up within several months after cessation of exposure; severe chloracne, on the other hand, has been known to persist for as long as thirty years following the last exposure. Persons more responsive are those who are prone to develop acne vulgaris. If one's exposure to TCDD is severe enough, cysts form and, on occasion, inflammation and scarring will occur. If there is no medical history of chloracne, then the likelihood of a significant exposure to, or adverse health effects from, TCDD is remote. Hence, chloracne is the clinical marker of TCDD exposure.

Chronic exposures to TCDD lead to degeneration of the liver and thymus in experimental animals; one sensitive index of exposure is atrophy of the thymus. Porphyria, altered levels in serum enzymes and weight loss are also observed. Major organs to be affected are the liver, blood forming organs and the reticuloendothelial system. Progressive weight loss, the first clinical sign of toxicity in the monkey, may be accompanied by alopecia, facial edema and a dry, scaly dermatitis over the rest of the body.

---

*Sodium cacodylate is the sodium salt of cacodylic acid (hydroxydimethylarsine oxide)

The metabolism of TCDD in man is unknown, and for the present there is only limited information available on the metabolic pathways and metabolites that may occur in other mammals. TCDD is distributed equally among the fat and liver of mammals, to a lesser extent in the kidneys, and is eliminated via the feces. Samples of fat from beef cattle and samples of milk from cows that had grazed on 2,4,5-T-treated pasture or rangeland, in addition to human milk from an area where 2,4,5-T herbicides were used repeatedly over a period of twenty years, had small to undetectable (not more than 10 ppt) amounts of TCDD.

No clearly defined mutagenic effect has been observed in vitro with TCDD. TCDD does induce genetic changes by the Ames test with S typhimurium and E coli but not with repair-defective strains; there is no evidence (from dominant lethal and cytogenetic evaluations in rodents) that such changes occur in whole animals.

Of perhaps more relevance to man are the in vitro studies on mammalian cells – i.e.,HeLa; Balb-3T3, normal mouse fibroblasts; SV101, virus (SV40) – transformed 3T3 mouse fibroblasts; human foreskin fibroblasts; and normal human lymphocytes. No significant growth inhibition in the cell cultures nor discernible ultrastructural changes have been observed by electron microscopy.

The teratogenicity and fetotoxicity of TCDD were discovered in 1969, in the course of a study on the biological activity of 2,4,5-T. The sample being used was later found to be contaminated with TCDD. The incidence of cleft palate was greater in two particular mouse strains (C57BL/6 and AKR), while the C57BL/6 mouse and the rat developed a higher incidence of cystic kidney. All doses given the rat led to gastrointestinal hemorrhage in the fetus. The increased ratio of fetal liver to body weight in the mouse suggested that TCDD was fetotoxic in this particular species.

A majority of studies using high doses of 2,4,5-T with 0.1 ppm of TCDD or less showed cleft palate in mice, but no other species, and embryotoxicity in the mouse, rat, hamster, sheep, monkey and rabbit. There is no scientific evidence that 2,4-D, 2,4,5-T or TCDD has caused reproductive difficulties or hazards in the human. No conclusive evidence is yet available that phenoxy herbicides or TCDD are mutagenic or teratogenic in man.

TCDD can induce cancer or serve as a cancer promoter in some strains of rats and mice. In contrast to some other chemical carcinogens, the carcinogenicity is always accompanied by considerable systemic toxicity.

From an environmental view, TCDD breaks down rapidly on leaves of plants, in water and on the surface of soil, especially through the action of sunlight. In soil it generally has a half-life of about 230 days; some soil microorganisms can degrade it, especially if other chlorinated hydrocarbons are present.

EXPERIENCE IN MAN

One of the most extensive human experiences with the adverse effects of TCDD in man involves the residents of Seveso, Italy. In July of 1976, TCDD was accidentally released from the ICMESA* trichlorophenol synthesis plant when a safety disk in a steam-heated reactor vessel ruptured. The plume of reactor contents, including TCDD, rose 160 feet above the factory and fell in a cone-shaped pattern about a mile long and a half-mile wide. This is the largest single population to have been exposed to the compound. Over 37,000 persons were potentially exposed to varying doses.

Two years after the incident occurred, the acute and mid-term health effects were assessed; the mild chloracne, which occurred mainly in a small group of children, healed quickly. Subclinical peripheral nerve impairment was reported; there was also some liver involvement, but without apparent functional disorder. Neither immunoresponse nor susceptibility to infectious diseases was altered.

---

*Industrie Chimiche Meda Societa Anonima

The most recent progress report on the long-term epidemiologic survey of the residents of the Seveso area emphasizes the preliminary nature of their findings and reiterates the conclusions of prior investigators. Except for the skin, no organs or body functions were impaired. No derangement of gestation, no fetal lethality and loss, no gross malformations, no growth retardation at term and no cytogenetic abnormalities have yet occurred.

The first of several accidental releases of TCDD and other dioxins, attending the manufacture of 2,4,5-trichlorophenol (TCP) or 2,4,5-T occurred in 1949 in the United States. At least 11 other industrial accidents or exposure incidents have occurred since then, both here and abroad. To date, an estimated 579 workers are known to have been exposed, including 156 employees in the ICMESA plant at Seveso.

CURRENT STUDIES

There are now a number of studies underway by agencies of the U. S. government and industry, which may resolve questions on the kinds and extent of human damage from exposure to low levels of TCDD:

> Through its Department of Environmental and Drug-Induced Pathology, the Armed Forces Institute of Pathology (AFIP) is examining biopsy and autopsy tissue of all Vietnam veterans. To date, only 152 cases have been assessed: the dominant diseases are epidermal inclusion cysts and chronic, non-specific dermatitis. If any malignancies were to have been induced by TCDD, they should be appearing by now, yet there have been no unusual morphological features nor clustering of tumors by diagnosis or site as to implicate Agent Orange.
>
> A soft-tissue sarcoma study also has been proposed that will be conducted jointly by the Armed Forces Institute of Pathology and the National Cancer Institute.
>
> The Air Force, through Project Ranch Hand, will administer and examine the 1,200 personnel who were involved in the actual handling and spraying of Agent Orange. They, and the control population of 20,000, are to be followed over the next twenty years.
>
> The University of California, Los Angeles, was awarded a contract by the Veterans Administration for the design of an epidemiologic study of Vietnam veterans.
>
> Approximately 45,000 Vietnam veterans who expressed concern about the hazards of Agent Orange have been examined by the VA; data on 25,000 of these men have been placed in a special Agent Orange Registry, which may serve later to identify them and to provide medical information as well as indications of health trends over the long term.
>
> The Chloracne Task Force was established to sift out those cases of dermatitis that either resemble or are truly chloracne. Cases of the former type will be reexamined by dermatologists who have an expert knowledge of the disease. Thus far, there are only 700 cases of "skin conditions" out of the total of 3,500 filed claims for damage from Agent Orange.

RECOMMENDATIONS:

The Council on Scientific Affairs recommends that:

1. The above studies on exposed, or allegedly exposed, persons continue to be supported and, if feasible, enlarged to include the cooperative engagement of all internationally known exposure data, as recommended by the International Agency for Research on Cancer (IARC).
2. All physicians be alerted through AMA publications to the classical signs of chloracne and the possible signs and adverse effects of TCDD exposure. They should be encouraged to enlist in the present efforts to identify and treat those persons who have had serious exposures to TCDD, and to cooperate in the collection of vital information that is needed for the ongoing human epidemiologic studies.

STATEMENT OF
FRANZ M. ENZINGER, M.D.
ARMED FORCES INSTITUTE OF PATHOLOGY
BEFORE THE COMMITTEE ON VETERANS AFFAIRS
UNITED STATES HOUSE OF REPRESENTATIVES
ON SOFT TISSUE SARCOMAS
12 July 1983

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE:

My name is Franz M. Enzinger. I am a pathologist and I am Chairman of the Department of Soft Tissue Pathology at the Armed Forces Institute of Pathology in Washington, D.C.

As consultant in soft tissue pathology to the military, Veterans Administration and civilian pathologists, I have had the opportunity to review and study a large number of soft tissue sarcomas, and over the past 24 years I have examined and diagnosed approximately 30,000 soft tissue sarcomas that were submitted for consultation to the Armed Forces Institute of Pathology. I also have been responsible for the preparation of an international classification of soft tissue tumors for the World Health Organization and for a textbook on the pathology of soft tissue tumors.

Although I cannot provide you with any new insight or specific information on the possible relationship of Agent Orange and soft tissue sarcomas, I would like to give you some background information on the occurrence, distribution and clinical behavior of these tumors.

Soft tissue sarcomas, compared to carcinomas and other forms of cancer, are relatively rare tumors. It is estimated that they account for about 0.8 to 1.0 percent of all cancers and that about 7000 to 8000 new cases are diagnosed each year in the United States. It has been suggested that there is an upward trend in the number of soft tissue sarcomas, but this is a true increase in part only and may reflect better access to medical facilities, better diagnostic capabilities and greater interest in this type of tumor. Incidence and distribution seem to be similar in different geographic regions of the world.

As the name indicates, soft tissue sarcomas usually arise in muscle, fat and fibrous connective tissue such as tendons or ligaments and less frequently in blood vessels and nerves that serve these tissues. Consequently, these tumors may occur anywhere, but the majority originates in the large muscles of the legs and arms where they often grow into poorly circumscribed, bulky tumors that infiltrate and destroy surrounding tissues. Despite their frequent large size and destructive growth, most of the tumors are painless and as a result recognition and therapy is often delayed for several months or even years. Soft tissue sarcomas occur at any age. About 15 percent affect persons younger than 15 years and about 35 percent persons 55 years or older. There is no particular sex prevalence. Some types are more common in men, others in women. There is no proven racial variation, even though the annual age-adjusted incidence rates have been reported to be higher for blacks than whites.

At the operating table, soft tissue sarcomas display a fairly uniform picture but when examined under the microscope they vary greatly in appearance and actually comprise a diverse and complex group of tumors rather than a single entity. At present, pathologists are able to recognize 25 major types and about 120 subtypes of this tumor, but there are still other types of soft tissue sarcomas that are as yet not clearly defined. The latter frequently cause considerable problems in diagnosis and may require examination with sophisticated techniques such as immunohistochemical preparations or the electron microscope. The various types are named according to the predominant cellular elements and the resemblance of the tumor to normal tissue or its embryonic counterpart. The most common types of soft tissue sarcomas are malignant fibrous histiocytoma, liposarcoma and fibrosarcoma which together account for slightly more than 50 percent of all cases. Malignant lymphoma, Hodgkin's disease and leukemia, the malignant tumors of lymph nodes and blood-forming organs, are not counted among the soft tissue sarcomas.

The various types differ considerably in the grade of malignancy, and identification and diagnosis of the exact microscopic type and subtype is not only essential for prediction of the clinical course and therapeutic response but also for selection and planning of therapy - the important decision whether a given sarcoma should be treated by local excision, radical local excision or amputation and whether surgery should be combined with radiotherapy or chemotherapy. If adequate treatment is given, many soft tissue sarcomas, particularly those occurring in infants and children, are curable, but even with the best type of therapy 35 to 40 percent of all patients with this tumor die of metastatic disease within five years after diagnosis, often after they have recurred locally. Yet without doubt some progress has been made in the therapy of soft tissue sarcomas over the past 10 years and overall survival rates have increased by at least 10 to 15 percent.

As with other forms of cancer, very little is known about the various causes of soft tissue sarcomas. A hereditary or genetic factor plays a role in a small proportion of cases, the majority of which are patients that develop sarcomas in a setting of neurofibromatosis. Such a factor is also suggested by the clustering of childhood sarcomas in some families. Moreover, there are sarcomas that seem to be induced by genetically determined or acquired immunodeficiency or therapeutic immunosuppression, a necessary procedure in organ tranplantation. Viruses are responsible for the induction of sarcomas in chicken, cats and mice, but there is no evidence so far that human viruses constitute a major risk factor in the development of soft tissue sarcomas. However, using the electron microscope, possible virus particles have been found in some cases.

There is even less reliable information on the significance of environmental factors. A small number of soft tissue sarcomas occur following radiation exposure, usually given as treatment for some other kind of malignant tumor, such as breast carcinoma or Hodgkin's disease. Most of the radiation-induced sarcomas are osteosarcomas, malignant fibrous histiocytomas and fibrosarcomas. Others develop in individuals who have a history of industrial or environmental exposure to vinyl chloride or asbestos. As a rule, specific risk factors, such as vinyl chloride, are associated with a single type of sarcoma (angiosarcoma) and none of the known risk factors seem to induce all types of sarcomas equally. Evaluation of the exact cause is often extremely difficult because of the possible effect of multiple environmental factors and the long time-lag or latent period between exposure and development of the tumor. Radiation induced soft tissue sarcomas, for example, frequently have a time-lag of 5, 10 or even more years. Asbestos related tumors may appear in some patients 30 or 40 years after the initial exposure.

As a soft tissue pathologist, I am of course familiar with the reported studies linking toxic, dioxin containing phenoxy herbicides with the development of soft tissue sarcomas. The suggested link, however, is mainly based on the observations of one group of Swedish investigators and there are other studies which viewed individually have not confirmed these findings. In my opinion, additional data are clearly necessary to resolve the question of a direct causal relationship between Agent Orange and soft tissue sarcoma. For this purpose, well-planned and carefully executed cooperative studies on a large number of patients with soft tissue sarcomas are needed.

Recently, the Veterans Administration has asked the Armed Forces Institute of Pathology to supply them with diagnoses and identification of at least 500 soft tissue sarcomas. Selection will be restricted to males who were diagnosed between 1975 and 1980 and were age 20 to 40 years at the time of diagnosis. These cases will be analyzed in regard to survival in Vietnam and exposure to various environmental factors and will be compared with two sets of matched controls of cancer and non-cancer patients. An epidemiologist and a biostatistician have been assigned to carry out this project.

I believe that this and other similar studies, that are currently being carried out, will make it possible to provide a satisfactory answer to the question whether or not exposure to Agent Orange plays a significant and specific role in the development of soft tissue sarcomas.

This concludes my statement, Mr. Chairman. I will be happy to answer any questions the committee may have.

7/6/83

Mr. Chairman and Members of the Subcommittee:

My name is Michael Luster. I am a scientist with the National Institite of Environmental Health Sciences (a component of the National Institutes of Health). My field of research interest is immunology. For the past seven years I have conducted research investigating the immunological changes that occur following exposure to various chemicals of environmental concern including dioxin (TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin) in rodents. I have published a number of scientific papers on the subject.

I am here today at your request to discuss the immunological effects of dioxin in laboratory animals. As was communicated to the subcommittee staff, I have no expertise with regard to the details of H.R.1961 and therefore am not prepared to discuss it.

What follows is a brief summary of what is known about the effects of dioxin on the immune system of laboratory animals. Following my formal remarks, I ask that the subcommittee include a more detailed review article as part of the hearing record.(1)

Animal studies have clearly demonstrated that dioxin may alter components of the immune system in a number of laboratory animal species. Animals exposed early in life, either prenatally or postnatally, appear more immunologically compromised than animals exposed as adults in that a variety of immune responses appear altered. In contrast, animals exposed during adult life demonstrate only depression of antibody synthesis. There is some evidence in laboratory animals that low doses of TCDD stimulate immune responses while higher doses produce immunosuppression, a phenomenon also seen with other chemicals. It has been reported that studies of immune function in Seveso children with cloracne revealed either no effect or a mild stimulation. If these data are correct (details of the data remain unpublished and they need independent review), one may speculate that chloracne is an earlier sign of acute TCDD toxicity than is immune depression. Draft reports of immunological studies of English workers industrially exposed to TCDD remain unpublished, unconfirmed, and report incomplete data. Thus, interpretation of the reported findings is not possible.

Thank you. This concludes my testimony. I would be happy to answer any questions you may have.

(1)Vos, J.G., Faith, R.E. and Luster, M.I.: Immune Alterations. In Halogenated Biphenyls, Terphenyls, Napthalenes, Dibenzodioxins and Related Products. R.D. Kimbrough (ed.), Raven Press, New York, N.Y., 1980, pp. 241-266, Chap. 8.

CHAPTER 8

Immune alterations

J.G. VOS
Laboratory of Pathology, National Institute of Public Health,
Bilthoven, The Netherlands

R.E. FAITH
Biomedical Research Center, Oral Roberts University,
Tulsa, Oklahoma, U.S.A.

and

M.I. LUSTER
Environmental Chemistry Branch, National Institute of Environmental Health Sciences,
Research Triangle Park, NC 27709, U.S.A.

8.1. Introduction

Interest in the influence of chemicals on the immune system has increased markedly in recent years, as a growing number of compounds have been shown to alter immunocompetence. Most attention has been given to chemicals of environmental concern that decrease the immunological responsiveness or increase the susceptibility to infection or tumor cell challenge. This is particularly true for polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs) and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Much less information is present on the immunotoxicity of 2,3,7,8-tetrachlorodibenzofuran (TCDF), while no data are reported for halogenated terphenyls and naphthalenes.

After a short overview of the immune system, the immune effects as produced in different species and with different exposure regimens will be discussed, and an attempt will be made to provide some insight into the complex action of the various chemicals on immunocompetence.

Effects on weight and histology of lymphoid organs are discussed in Chapter 5.

8.2. The immune system

The immune response comprises all the phenomena that result from the interaction of cells of the immune system with antigen. A fundamental characteristic of specific immunity is the establishment of immunological memory: the first contact with the antigen (e.g. an infectious organism) imprints specific information. Upon a second contact with the same organism, a so-called secondary immune response will occur.

Kimbrough (ed.) Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products
© *Elsevier/North-Holland Biomedical Press 1980*

In addition to specific immunity, the body is also protected by nonspecific resistance. This nonspecific protective mechanism includes: certain microbial inhibitors (e.g. lysozyme), the interferon system as a defense against viruses, and the phagocytosis of particles (e.g. bacteria) by polymorphonuclear leukocytes and macrophages, which is particularly enhanced during the acute inflammatory response to foreign organisms. Regarding the nonspecific immunity, the complement system should also be mentioned. Normally, the complement system can be activated by an antigen–antibody complex, leading to a cytotoxic reaction (cell lysis) when the antigen is a cell. However, complement can also be activated by other processes, e.g. by certain bacterial factors such as endotoxin and protein A, via the properdin pathway.

There is now abundant evidence (see Humphrey and White, 1970; Greaves et al., 1973; Roitt, 1974) indicating that there are two distinct but not entirely independent systems of specific immunity (Fig. 8.1). One is cell-mediated immunity, which comprises those reactions which operate by specifically sensitized lymphocytes and are transferable by these cells. It includes the following immune processes: (1) classical cell-mediated protective immunity, which is predominantly effective against fungi, viruses, and a number of bacteria; (2) delayed-type hypersensitivity (e.g. tuberculin hypersensitivity or contact hypersensitivity); (3) the rejection of tumors and foreign tissues such as transplants (allografts); (4) allogeneic (graft vs. host) disease.

The other system of specific immunity is the humoral immunity which operates by antibody-producing cells. This type of immunity is transferable by serum and includes: (1) classical antibody-mediated protective immunity, which combats bacteria and a number of viruses, and (2) immediate hypersensitivity reactions (anaphylactic type, cytotoxic type, and complex-mediated type).

Experimental and clinical (immune deficiency diseases in man) observations (reviewed by Greaves et al., 1973) have revealed the dichotomy of the immune system. Surgical removal of the bursa of Fabricius in birds impairs antibody synthesis, but does not affect allograft rejection or graft vs. host reaction. On the other hand, neonatal thymectomy impairs cell-mediated immune reactions. Lymphocytes play a central role in both types of immune response, but these lymphocytes consist of two distinct populations with different functions and properties. The precursor cells of the lymphocytes (the so-called hemopoietic stem cells) migrate in the embryo from the yolk sac through the liver to the bone marrow. Cells that eventually become immunocompetent lymphocytes mature outside the bone marrow. Some enter the thymus (Fig. 8.1), where they proliferate and mature under the influence of the thymic epithelial cells (possibly by direct contact and/or thymic hormones). A small population of lymphocytes are released from the thymus and are called T cells (thymus-derived lymphocytes). The T cells circulate through the body and temporarily reside in special so-called thymus-dependent areas in the white pulp of the spleen (periarteriolar lymphocyte sheaths, PALS) and lymph nodes (paracortical area).

Stimulation of T cells by most antigens occurs after processing of the antigen by

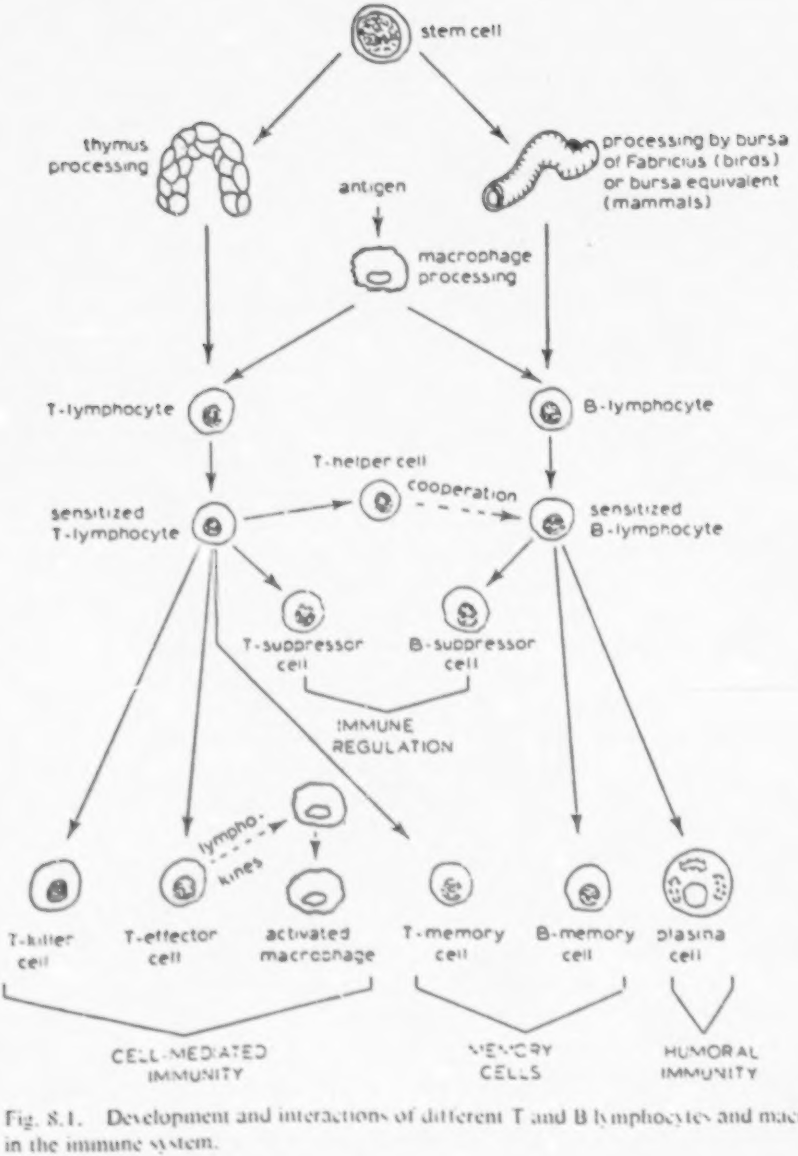

stem cell
thymus processing
processing by bursa of Fabricius (birds) or bursa equivalent (mammals)
antigen
macrophage processing
T-lymphocyte
B-lymphocyte
T-helper cell
cooperation
sensitized T-lymphocyte
sensitized B-lymphocyte
T-suppressor cell
B-suppressor cell
IMMUNE REGULATION
lympho-kines
T-killer cell
T-effector cell
activated macrophage
T-memory cell
B-memory cell
plasma cell
CELL-MEDIATED IMMUNITY
MEMORY CELLS
HUMORAL IMMUNITY

Fig. 8.1. Development and interactions of different T and B lymphocytes and macrophages in the immune system.

macrophages. These antigen-specific reactive cells divide and produce a pool of sensitized T lymphocytes. Sensitized T cells can function as memory cells, effector cells, killer cells, helper cells and suppressor cells. In delayed-type hypersensitivity, effector cells produce biologically active products (lymphokines). Some of these soluble lymphocyte factors, e.g. migration inhibition factor (MIF), chemotactic factor (CF) and macrophage-activating factor (MAF), have profound effects on the macrophage functions. Killer cells are cytotoxic and have a key role in the rejection of tumor cells and transplants. As will be discussed later, T helper cells collaborate with B cells in antibody production against most antigens. Suppressor T cells function to suppress the activity of B cells (Taylor and Basten, 1976) or effector T cells (Asherson and Zembala, 1976). In addition, there are indications for the presence of B cells that suppress T cells (Turk et al., 1976). Suppressor and helper cells play a major role in the regulation of an immune response.

The bursa of Fabricius in birds or the bursa-equivalent in mammals (possibly gut-associated lymphoid tissue or bone marrow) acts as a central lymphoid organ in which stem cells are induced to become (bursa-derived) B cells (Fig. 8.1). B cells circulate and temporarily reside in the thymus-independent areas of the spleen (follicles and peripheral regions of the white pulp) and lymph nodes (follicles and medulla). Upon antigenic stimulation, B cells specific for that particular antigen proliferate and develop into plasma cells that secrete antibody or serve as memory cells. The main immunoglobulin (Ig) classes are IgG, IgA and IgM. IgG is the most abundant antibody and is primarily synthetized during the secondary response. It diffuses readily into the extravascular tissue where it combats microorganisms and their toxins. IgA is the major Ig in the sero-mucous secretion, and its task is to defend the external surfaces of the body. IgM is a high-molecular-weight antibody that is a very efficient agglutinator. IgM is produced early in the response to infection and is, therefore, the most effective first-line defense.

This division in the organization of the immune system does not imply that T and B cells are totally independent. For most antigens, cooperation between them is necessary for the generation of an antibody response (the so-called T cell-dependent humoral response), although the mechanism of this cooperation is not known. Cooperation by these T helper cells is not necessary for all antigens: type III pneumococcal polysaccharide and *E. coli* lipopolysaccharide are so-called thymus-independent antigens and can generate substantial antibody responses in nude, athymic mice. Dependency of T cell cooperation also varies with the class of immunoglobulins: the IgM response is less dependent on T helper cells than is the IgG response.

Fixed and free macrophages and their precursors (promonocytes in the bone marrow and monocytes in the blood) belong to the mononuclear phagocyte system (MPS) (Langevoort et al., 1970). Macrophages are intimately involved in the initiation phase and the effector phase of humoral and cell-mediated immune reactions. In contrast to lymphocytes they do not clonally divide and are not antigen specific (Pierce and Kapp, 1976). Processing of antigen by macrophages seems to be necessary: removal of macrophages from lymphocyte suspensions abrogates the induction of an immune response. Most antigens are rapidly broken down inside the macrophage, but some material is probably retained on the surface. This surface-bound antigen and perhaps a soluble factor from the macrophage interact with lymphocytes to induce an immune response.

Interactions of macrophages and sensitized lymphocytes in the effector phase of the cell-mediated immune response are probably mediated by the earlier mentioned lymphokines.

Different environmental, physiological and pathological conditions can either directly – or indirectly – effect the structural and functional capacity of the immune system. Therefore, in evaluating chemical effects on the immune system, these factors should be considered (see Vos, 1977). For example, when atrophy of thymus and peripheral lymphoid organs is found in a toxicity study at a toxic level where there is also a reduction in body weight, special attention should be given to the possibility that the atrophy is produced by undernutrition (Scrimshaw et al., 1968; Gontzea, 1974). An interaction of the chemical with the endocrine system should also be considered, since various hormones (in particular glucocorticosteroids) modify the immunological responsiveness (White and Goldstein, 1972).

8.3. Polychlorinated biphenyls (PCBs)

The first suggestion that PCBs might affect the immune system stemmed from general toxicity studies. In 1965 Flick et al. reported that ingestion of PCBs resulted in small spleens in chickens. Following this initial report, Vos and Koeman (1970) reported that ingestion of PCBs induced atrophy of lymphoid tissue in chicken. Similar effects on lymphoid tissue were also observed in the rabbit and guinea pig. Vos and Beems (1971) applied 118 mg of the three PCB preparations, Phenoclor DP6, Clophen A60 and Aroclor 1260, to the dorsal skin of rabbits 5 times a week for 38 days. Exposure to these PCB preparations resulted in lymphopenia, atrophy of the cortex of the thymus and a reduction in the number of germinal centers in the spleen and lymph nodes. Vos and van Driel-Grootenhuis (1972) fed guinea pigs varying levels (ranging from 0 to 250 mg/kg diet) of Clophen A60 and Aroclor 1260 for 4 or 6 weeks. At levels as low as 10 mg/kg in the feed both PCB preparations significantly reduced the numbers of circulating leukocytes and lymphocytes (see Table 8.1). In addition, there was a significant reduction in the relative thymus weight at the 50 mg/kg dosage level (see Table 8.2). A further indication that PCBs may affect immunocompetence was furnished by Friend and Trainer (1970) who showed that ducklings fed low levels of Aroclor 1254, while showing no overt signs of toxicity, were more susceptible to challenge with duck hepatitis virus. The significance of this last report needs to be considered carefully as the interactions between hepatotoxins and liver pathogens may result in increased susceptibility following viral challenge without any dysfunction in immunity.

Studies have clearly shown that PCB exposure suppresses humoral immunity. Vos and de Roij (1972) and Vos and van Driel-Grootenhuis (1972) reported that chronic exposure of guinea pigs to Clophen A60 and Aroclor 1260 at levels as low as 50 mg/kg diet caused a significant reduction in antibody titers to tetanus toxoid (Table 8.1). Koller and Thigpen (1973) reported that chronic exposure of rabbits to 300 mg of Aroclor 1221, 1242 or 1254 resulted in a reduction of both primary and secondary

TABLE 8.1

Effect of PCB feeding on serum antitoxin values as measured by single radial immunodiffusion and on leukocyte counts in female guinea pigs stimulated with two doses of tetanus toxoid[a] (Adapted from Vos and van Driel-Grootenhuis, 1972).

Dietary concn. of PCB (mg/kg)	Tetanus antitoxin titers (AE/ml)	White blood cells (× 10^3/mm^3)	
		Leukocytes	Lymphocytes
0	69.9 ± 13.7	11.3 ± 1.4	5.9 ± 1.4
10 (Clophen A60)	57.6 ± 19.5	9.6 ± 3.3	5.2 ± 1.7
50 (Clophen A60)	40.2 ± 12.6[d]	7.1 ± 1.2[d]	4.6 ± 0.8[b]
50 (Aroclor 1260)	41.4 ± 17.0[d]	6.4 ± 1.5[d]	4.1 ± 0.9[c]

a. Mean values ± S.D. of 9–10 animals per group. The antitoxin titers were expressed in International Units per ml (AE/ml) on the basis of the international standard of tetanus antitoxins.
b. $P \leq 0.025$.
c. $P \leq 0.01$.
d. $P \leq 0.005$.

TABLE 8.2

Effect of PCB feeding on skin reaction and thymus in Freund's Complete Adjuvant-stimulated female guinea pigs[a] (Adapted from Vos and van Driel-Grootenhuis, 1972).

Dietary concn. of PCB (mg/kg)	Skin reaction[b]		Thymus		
	24 h	48 h	Abs. weight	Body weight ratio (× 10^3)	% cortex[c]
0	11.6 ± 1.3	11.1 ± 1.2	0.97 ± 0.13	2.0 ± 0.4	72.7 ± 6.7
50	8.0 ± 1.4[f]	6.9 ± 1.6[f]	0.74 ± 0.09[f]	1.7 ± 0.2[d]	65.2 ± 4.7[e]

a. Mean values ± S.D. of 10 animals per group.
b. Diameter of skin reaction (in mm) measured 24 and 48 h after tuberculination.
c. Relative surface estimation of the cortex.
d. $P \leq 0.05$.
e. $P \leq 0.01$.
f. $P \leq 0.005$.

antibody titers, following immunization with pseudorabies virus. However, Street and Sharma (1975) observed no effect on antibody titers in rabbits to sheep red blood cells (SRBCs) following chronic exposure to Aroclor 1254, although, it should be noted that the dosage levels utilized in the latter study were lower than those employed by Koller and Thigpen. Loose and coworkers (1977) reported that chronic exposure of mice to 167 mg of Aroclor 1242 per kg diet suppresses both primary and secondary antibody responses to sheep red blood cells and also abolishes memory cell function. Thomas and Hinsdill (1978) reported that rhesus monkeys chronically fed 5 mg Aroclor 1248 per kg diet had significantly lower antibody titers when immunized with sheep red blood cells; however, these animals mounted a normal antibody response to tetanus toxoid. Loose et al. (1977) and Thomas and Hinsdill (1980) also reported that PCB exposure lowers circulating immunoglobulin levels.

While the suppressive effects of PCBs on humoral immunity are well documented, the affects on cellular immunity are less clear. Vos and van Driel-Grootenhuis (1972) reported that guinea pigs chronically exposed to 50 mg PCBs/kg diet were suppressed in their delayed hypersensitivity reactions to tuberculin (Table 8.2).

In contrast, Street and Sharma (1975) reported that, while there was a trend towards lower skin reactivity to tuberculin with increasing PCB exposure in rabbits chronically exposed to PCBs in their feed, there were no significant differences between any dosage group and controls. It should be noted that the highest dosage level employed by Street and Sharma (170 mg/kg diet) was higher than the 50 mg/kg dosage level employed by Vos and van Driel-Grootenhuis. Bonnyns and Bastomsky (1976) reported that short-term exposure of rats to 250 mg Aroclor 1254 per kg diet resulted in an enhanced responsiveness of peripheral blood lymphocytes to stimulation by the T cell mitogen phytohemagglutinin (PHA) which may indicate an affect on regulatory cell function. Similarly, Silkworth and Loose (1979) reported that exposure of mice to 167 mg/kg feed for 41 weeks resulted in increased responsiveness of splenic lymphocytes to in vitro mitogen stimulation as well as the allogeneic response in mixed lymphocyte cultures. Earlier Silkworth and Loose (1978) reported that exposure of mice to 167 mg of PCBs per kg diet enhanced graft vs. host reactions by spleen cells.

Other parameters studied with PCBs have dealt with host resistance to infectious challenge. Loose et al. (1978) reported that mice fed a diet containing 167 mg PCBs/kg for 3 weeks were more susceptible following challenge with *Plasmodium berghei* than were unexposed control animals. Smith et al. (1978) reported that exposure of mice either acutely or subacutely to levels of Aroclor 1254 ranging from 0.3 to 75 mg/kg body weight resulted in a decreased ability to clear *Listeria monocytogenes* from circulation. Thomas and Hinsdill (1978) found that mice fed 1000 mg Aroclor 1248/kg diet for 3 to 5 weeks were more susceptible to challenge with *Salmonella typhimurium*, as measured by increased numbers of viable organisms in liver, spleen and blood. Loose et al. (1978) and Thomas and Hinsdill (1978) reported that exposure of mice to PCBs enhanced susceptibility to endotoxin shock, which may suggest an impaired macrophage function, since the primary pathway for endotoxin detoxification is thought to be a macrophage-dependent process (Braude et al., 1955). In this respect, Aroclor 1242 inhibits RNA synthesis in resting macrophages following in vitro exposure (Conradt et al., 1979). The susceptibility of transplantable tumors has also been examined in PCB exposed animals. Repeated i.p. injection of PCB (Aroclor 1254) in rats inhibited the transplantability and growth of Walker 256 carcinosarcoma (Kerkvliet and Kimeldorf, 1977) although Aroclors 1221, 1242 and 1254 did not promote or induce the oncogenesis of Moloney leukemia virus in mice (Koller, 1977).

8.4. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)

From an immunological standpoint, TCDD has been the most extensively studied halogenated aromatic hydrocarbon. Severe thymus atrophy has been reported to occur in almost all laboratory animals exposed to lethal or sublethal doses of TCDD. Of course, thymic atrophy is only an indication of immunosuppression since many toxic compounds or stressful events may induce thymic lesions although not necessarily to the same degree as TCDD. Histologically, the thymus in TCDD-exposed animals is characterized by depletion of lymphocytes throughout the cortex and lymphocyte necrosis has been observed early after exposure (Vos et al., 1973; Gupta et al., 1973; McConnell et al., 1978). The thymic medulla is not affected as severely as the cortex and in many respects appears similar to cortisone-induced atrophy of the thymus (reviewed by Bach, 1975). Interestingly, the thymic medulla is populated with mature T cells while the cortex contains pre-thymic or immature T cells (reviewed by Spreafico and Anacterio, 1977). Peripheral lymphopenia has been observed in laboratory animals following TCDD exposure, although fairly high dosages may be required (Zinkl et al., 1973; Vos et al., 1973). Elevated numbers of circulating lymphocytes have also been reported to occur following TCDD exposure (Weissberg and Zinkl, 1973). Alterations in the number of circulating lymphocytes should not be considered a criterion for immune dysfunction since suppressed cell mediated immunity has been reported at exposure levels that do not induce lymphopenia (Vos and Moore, 1974).

The immunologic effects following in vivo TCDD exposure in both the adult and neonatal animal have been well characterized. Guinea pigs exposed to as little as 40 ng TCDD per kg body weight weekly for 8 weeks had depressed delayed hypersensitivity reactions to tuberculin (Vos et al., 1973). In addition, the secondary, although not primary, antibody response to tetanus toxoid was depressed at higher dosages. In mice, graft vs. host reactivity was suppressed following dosages of 0.5 μg/kg body weight weekly for 4 weeks (Vos et al., 1973), while lymphoproliferative responses following stimulation with PHA were decreased only at the 25 μg/kg level (Vos and Moore, 1974). Sharma et al. (1978) reported that a number of immunological parameters were effected in mice and rabbits following exposure to low levels of TCDD (less than 1.0 μg/kg/week for 8 weeks). These included decreases in lymphoproliferative response to lymphocyte mitogens (at levels as low as 0.1 μg/kg) and decreases in antibody response (tetanus toxoid), skin reactivity (tuberculin) and serum immunoglobulin levels at dosages of 1.0 μg/kg body weight. Dietary feeding of mice with levels as low as 10 μg TCDD/kg reduced serum γ-globulin, primary and secondary antibody titers to SRBC, delayed-type hypersensitivity reactions and enhanced the susceptibility to *Salmonella* infection (Hinsdill et al., 1980).

A recent report has described the immune status of 44 children (20 had chloracne) who resided in the immediate area of the TCDD contamination in Seveso, Italy (Reggiani, 1978). These studies found no abnormalities in serum immunoglobulin concentrations, circulating levels of complement and lymphoproliferative responses of T and B cells following mitogen stimulation (see also Chapter 9B2).

TCDD administered during the pre/postnatal or postnatal period via maternal dosing has been reported to cause severe effects on the immune system in both mice and rats and may be a prerequisite for TCDD-induced suppression at least in the rat. Dosage of 5.0 μg/kg in mice and rats on various days of gestation and weaning suppresses a variety of cell-mediated immune correlates including proliferative responses of phytohemagglutinin (PHA)- and concanavalin A (Con A)-stimulated splenic and thymic lymphocytes (Vos and Moore, 1974; Faith and Moore, 1977; Luster et al., 1979c), delayed hypersensitivity reactions (Moore and Faith, 1976; Faith and Moore, 1977; Luster et al., 1979c; Thomas and Hinsdill, 1979), graft vs. host reactivity of spleen cells (Vos and Moore, 1974) and the ability to reject skin allografts (Vos and Moore, 1974). As would be expected, the affects are more severe when the chemical is administered during the pre- and postnatal periods than if administered solely in postnatal life (Vos and Moore, 1974; Faith et al., 1978; Luster et al., 1979c). Furthermore, the effects are relatively long-lasting, persisting up to 4 months of age (Faith et al., 1978; Luster et al., 1979c).

TCDD affects humoral immune responses but apparently requires higher doses than that which induces defects in cell-mediated immunity. As previously mentioned, TCDD exposure causes reduction of serum γ-globulin levels and antibody responses to tetanus toxoid in adult guinea pigs (secondary only) (Vos et al., 1973), rabbits, mice (Sharma et al., 1978) and plaque-forming cell (PFC) responses to SRBCs in perinatally exposed mice (Thomas and Hinsdill, 1979). Fetal and/or neonatally exposed rats respond normally to bovine γ-globulin as measured by passive hemagglutination although lymphoproliferative responses following stimulation with T cell mitogens and delayed hypersensitivity reactions are severely depressed (Faith and Moore, 1977; Luster et al., 1979c). These studies suggested that TCDD induced suppression of T cell functions was selective in that T helper cell function was not affected (Faith and Moore, 1977). Further studies in which normal antibody responses in neonatally thymectomized rats occurred following adoptive transfer of bovine γ-globulin-primed T cells from postnatally TCDD-treated rats further confirmed these observations (Faith et al., 1978). The lymphoproliferative response to the B cell mitogen, lipopolysaccharide (LPS), were depressed in mice exposed pre/postnatally to TCDD, but required exposure levels higher than that which caused suppression of T cell mitogenic responses (Luster et al., 1979c). Lymphoproliferative responses following stimulation with LPS and antibody responses to LPS reside in distinct B cell populations and thus should not be considered synonymous (Poe and Michael, 1976).

Thigpen et al. (1975) reported that subclinical doses of TCDD in mice (1.0 μg/kg/week for 4 weeks) followed by infection with *Salmonella bern* resulted in increased mortality and decreased time from infection to death. Infection by *Herpes suis* (Pseudorabies) did not effect mortality. It was subsequently observed that mice treated with single or repeated doses of TCDD revealed a marked increase in susceptibility to endotoxin from gram negative bacteria (Vos et al., 1978). The decreased resistance of TCDD-exposed mice to infection with *Salmonella* but not *Pseudorabies* was, thus, suspected to be due to the endotoxin content of the bacteria rather than a defect in cell mediated immunity, especially since endotoxin hypersensitivity was recorded below the dose level that produced thymus atrophy. A similar observation was recently made by Thomas and Hinsdill (1979) who found increased susceptibility to endotoxin in the offspring from mice that were exposed to TCDD by maternal feeding at dietary levels as low as 1 μg/kg. A recent study in prenatal exposed mice has shown a decreased resistance to non-endotoxin-producing bacterium, *Listeria monocytogenes*. However, significantly decreased resistance to infection was not found at TCDD dosage levels that did not induce thymic atrophy or depression of cell-mediated immune parameters (Table 8.3; Luster et al., in preparation). In contrast, Thomas and Hinsdill (1979) reported that perinatal exposure of mice by maternal feeding up to 5 μg TCDD/kg did not render the animals more susceptible to a challenge with *L. monocytogenes* but did induce thymus atrophy and depress delayed hypersensitivity reactions.

The increased sensitivity to endotoxin shock seen with TCDD must nonetheless be considered as a possible cause of death in TCDD toxicity (Table 8.4). The phenomenon is of particular interest when considered in connection with terminal hemorrhages observed in TCDD-exposed rats, mice and guinea pigs, thrombocytopenia observed in rat and guinea pigs, and the presence of thrombi in blood

TABLE 8.3
Effects of pre/postnatal exposure of TCDD via maternal dosing on various immunological functions in mice (From Luster et al., 1980).

Dosage (μg/kg)[a]	Body weight (g)	Thymus/ body weight (× 10³)	Lymphoproliferative responses (Δcpm × 10³)		Colony-forming units in spleen	Incidence of mortality to *Listeria* (%)[b]
			PHA	LPS		
0	13.6 ± 0.2	4.4 ± 0.3	31.4 ± 3.9	3.8 ± 0.5	10.3 ± 1.0	7/25 (28%)
1.0	12.6 ± 0.4 (8↓)[c]	4.6 ± 0.2 (4↑)	35.9 ± 3.4 (14↑)	4.6 ± 0.5 (21↑)	n.d.[d]	6/15 (40%)
5.0	10.9 ± 0.4[f] (19↓)	3.3 ± 0.2[e] (25↓)	14.9 ± 3.2[e] (53↓)	3.1 ± 0.3 (18↓)	7.0 ± 0.5[e] (32↓)	11/15 (73%)[e]
15.0	7.9 ± 0.5[f] (41↓)	1.8 ± 0.2[f] (59↓)	13.3 ± 3.2[f] (58↓)	2.8 ± 0.2 (26↓)	3.8 ± 0.3[f] (63↓)	n.d.

a. Pregnant C57Bl/6 mice mated to C_3H mice were intubated orally on day 14 of gestation and day 1, 7 and 14 after birth with 0, 1.0, 5.0 or 15.0 μg TCDD/kg body weight. Mean values ± S.E. of a minimum of 8 animals per group.

b. Mice were injected intravenously with 1.2×10^6 viable organisms and mortality scored after 14 days.

c. Percent difference from controls.

d. n.d. = not done.

e. $P < 0.05$.

f. $P < 0.01$.

TABLE 8.4
Effect of four weekly doses of TCDD on the susceptibility of mice to endotoxin (From Vos et al., 1978).

Dose of TCDD (µg/kg)[a]	Incidence of mortality[b]		
	10 µg endotoxin	250 µg endotoxin	
0	0/4	0/5	
1.5	0/4	1/5	
5.0	0/4	6/6	
15.0	1/4	6/6	
50.0	2/4	n.d.[c]	
	10 µg endotoxin	100 µg endotoxin	500 µg endotoxin
0	0/6	0/6	2/6
1.5	0/6	1/6	3/6
50.0	2/5	5/6	6/6

a. Male outbred Swiss mice (3–4 weeks of age) were intubated orally, once a week for 4 weeks, with TCDD in acetone–arachis oil carrier.

b. Intravenous injection with endotoxin (*E. coli* LPS 0127:B8) 48 h after last intubation. Mortality scored after 48 h.

c. n.d. = not done.

vessels of heart and lung in lethally exposed rats, since these lesions also occur in endotoxin shock (see Vos, 1978).

Several investigators have attempted to determine the effects of TCDD, if any, on macrophages. These studies have been prompted by the increased endotoxin sensitivity observed following TCDD treatment in mice since the primary pathway of endotoxin detoxification is thought to be a macrophage-dependent process (Braude et al., 1955). Exposure of adult mice to relatively high levels of TCDD (50 µg/kg/week for 4 weeks) did not effect their ability to kill non-specifically or to phagocytize *Listeria monocytogenes* nor alter the reduction of nitro-blue tetrazolium by resident peritoneal macrophages (a measure of non-activated macrophages) (Vos et al., 1978). Thioglycollate-induced peritoneal macrophages from pre/postnatally TCDD-exposed mice were capable of phagocytizing SRBCs normally, had normal levels of acid phosphatase, and responded normally to colony stimulating factor in vitro (a measure of macrophage proliferation) (Luster et al., in preparation). Studies also have been undertaken to determine whether pre/postnatal TCDD exposure in mice stimulates production of a suppressor macrophage population. Removal of adherent cells from spleens of pre/postnatally TCDD-exposed mice by passage over Sephadex G-10 columns (< 0.2% esterase positive) failed to restore normal lymphoproliferative responses following stimulation with T cell mitogens. Furthermore, co-culturing lung or peritoneal macrophages from treated mice with macrophage-depleted spleen cells from normal mice did not suppress lymphoproliferative responses. These studies suggested that suppressor macrophages probably do not play a role in the T cell defect following TCDD treatment. Recently (personal communication, J.E. Thigpen, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709, U.S.A.), a reduced number of peritoneal leukocytes (both lymphocytes and monocytes) was noted 5 days following induction with thioglycollate in mice exposed to low levels of TCDD as adults. While the significance of this finding is presently unknown, it is interesting to note that similar observations have been reported following treatment with cyclophosphamide (Godeberg et al., 1975). Although macrophage functions do not appear severely altered by TCDD, it is still conceivable that the increased susceptibility to endotoxin may be due to a yet undetermined TCDD-induced macrophage defect involved directly in detoxification.

Attempts have been made to elucidate the mechanism(s) responsible for TCDD-induced immunosuppression. While, in general, these studies have not culminated in definitive findings, they have provided valuable information into the relationship between TCDD and the immune system. Early studies indicated that the atrophy of the thymus by TCDD is not indirectly mediated by altered pituitary or adrenal functions since thymic atrophy occurs in adrenalectomized or hypophysectomized rats treated with TCDD (van Logten et al., 1980). Furthermore, normal levels of circulating corticosteroids can be found in immunosuppressed TCDD-treated guinea pigs (Vos et al., 1973). TCDD treated mice have also been found to contain normal serum levels of zinc (Vos et al., 1978). TCDD-induced thymic atrophy is not caused by reduced food intake (van Logten et al., in preparation) or alterations of serum α-fetoprotein (Vos and Boekestein, unpublished data). Treatment of exposed mice with thymosin, a thymic hormone which plays a vital role in T cell maturation, does not restore normal thymic architecture nor lymphoproliferative response of thymocytes to T cell mitogens (Vos et al., 1978). This may be indicative that immunosuppression is not due to a defect in T cell maturation. It was reported in an earlier review that serum from pre/postnatally exposed rats suppressed the in vitro lymphoproliferative responses of normal rat spleen cells, which would indicate a cytotoxic factor was present in serum from exposed animals (Faith et al., 1980). However, we have been unable to confirm these findings using serum from pre/postnatally exposed immunosuppressed mice (Luster et al., unpublished data).

One of our laboratories have screened for suppressor cell activity in pre/postnatally exposed mice (Luster et al., 1980). These studies were prompted by recent findings that a high incidence of immunosuppressed cancer patients and tumor-bearing animals possess a sub-population of cells residing in either the B, T or macrophage cell populations capable of producing soluble factors which suppress the immune system. Cocultivation experiments in which spleen cells from normal mice were cultured with spleen cells from TCDD-treated mice which had previously been treated with either anti-T cell antisera plus complement (to destroy T cells) or mitomycin C (to block DNA synthesis but not production of suppressor factors) failed to suppress lymphoproliferative responses of normal spleen cells when compared to spleen cells from similarly treated normal mice (Luster et al., 1980). These studies indicated that while the defective cell type resided in the T cell population, no suppressor cell activity was produced. Lymphocyte homing studies have been conducted in rats exposed pre/postnatally to TCDD (Faith and Luster, 1979). While the alterations were primarily focused on thymocytes, the studies indicated that TCDD altered normal homing patterns of lymphocytes from treated rats when adoptively transferred to untreated rats as well as lymphocytes from normal rats when transferred into treated recipients.

A number of studies have attempted to study the direct effects of TCDD on lymphocytes by in vitro exposure. In vitro studies have often been hampered by the insolubility of TCDD in physiological buffers (Matsumura and Benezet, 1973). It was found that 100 ng of TCDD was only 5% soluble in 1 ml solution containing equal volumes of dimethylsulfoxide (DMSO) and phosphate-buffered saline, although addition of normal serum enhances the solubility (Luster, unpublished observations). Nonetheless, Kouri et al. (1975) showed that 0.1 ng of TCDD/ml of culture media was sufficient to induce aryl hydrocarbon hydroxylase activity in human lymphocyte cultures while Niwa et al. (1975) reported that 320 ng/ml of TCDD in media is toxic to human lymphocytes. Vos and Moore (1974) were unable to affect the lymphoproliferative response of spleen cells to T cell mitogens at concentrations up to 20 ng/ml in culture media. Luster et al. (1979b) reported that brief treatment of whole spleens with TCDD dissolved in DMSO (50 ng TCDD/ml) prior to culture severely suppressed the mitogenic response to PHA, Con A and LPS. However, these studies were hampered by the solubilizing agent (DMSO) which itself was somewhat lymphotoxic. These studies further noted that the ability of lymphocyte mitogens to bind to cell surface receptors was not effected by TCDD treatment suggesting that an active event is being effected by TCDD. In the light of these results, it is interesting to discuss the existence of a TCDD receptor in lymphocytes. In this respect, tissue distribution studies with [^{3}H]TCDD given orally in rats (Van Miller et al., 1976) and dibenzofurans in mice (Morita and Oishi, 1977) indicated that splenic retention was relatively high. Furthermore, Poland and Glover (1976) have provided evidence for a TCDD receptor present in hepatic cytosol, whose binding affinity corresponds with the induction of hepatic aryl hydrocarbon hydroxylase (AHH) activity. As mentioned previously, human lymphocyte cultures treated with TCDD induce AHH activity (Kouri et al., 1975). The recent finding of Carlstedt-Duke (1979) that of a number of organs studied (including the liver) rat thymus had the highest concentration of the TCDD receptor, is a strong argument in favour of the suggestion of Poland et al. (1979) that the initial event in the toxic action of TCDD (including thymus atrophy) is mediated through the cytosolic TCDD receptor.

Recently, the effects of TCDD-treatment on bone marrow stem cells have been examined in pre/postnatally exposed mice (Table 8.3; Luster et al., in preparation). Bone marrow cellularity and colony-forming units in culture (CFU-C) designed to measure macrophage-granulocyte progenitor cells were depressed only at lethal doses. Of particular interest, however, colony forming units in spleen (CFU-S) which measures pluripotent stem cells were suppressed at sublethal as well as lethal levels. This may indirectly suggest that lymphocyte progenitors are defective although erythrocyte precursors cannot be excluded. The data provides suggestive evidence that TCDD immunosuppression can be related to inhibition of lymphocyte maturation (possibly through the cytosolic TCDD receptor) and the site of this occurrence may at least in part be directed to the bone marrow.

8.5. 2,3,7,8-Tetrachlorodibenzofuran (TCDF)

TCDF is very similar to TCDD in chemical structure and is only slightly less toxic for guinea pigs and chickens than TCDD (Moore et al., 1976; McKinney et al., 1976). The pathology reported to occur following TCDF exposure is very similar to that following TCDD exposure (Gupta et al, 1973) and includes severe thymus atrophy. The similarity between TCDD and TCDF in chemical structure, toxicological effects and level of exposure necessary to induce effects would suggest that TCDF can also be immunosuppressive.

To date there has only been one reported study on the immune effects of TCDF. This is the study of Luster et al. (1979d) wherein adult guinea pigs were dosed by gavage once weekly with varying doses of TCDF for six weeks. At the highest dosage (1.0 μg/kg body weight/week) approximately 30% of the animals failed to survive. Survival was not affected at the lower dosage levels, nor were there any overt signs of toxicity.

TCDF exposure resulted in a trend toward reduced body weight gain and reduced circulating leukocyte counts. However, there were no significant differences between dosage groups and controls. Relative thymus weights were significantly reduced in the two highest dosage groups (1.0 and 0.5 μg/kg levels). A dose response effect appeared to occur in serum IgG levels and specific antibody titers to bovine γ-globulin; however, none of the dosage groups were significantly depressed. TCDF exposure depressed the ability of exposed animals to mount normal delayed hypersensitivity responses in vivo and the ability of lymphocytes to produce migration inhibition factor (MIF) in vitro. TCDF exposure also reduced the in vitro responsiveness of splenic lymphocytes from exposed animals to PHA and LPS but not Con A.

8.6. Polybrominated biphenyls (PBBs)

Vos and van Genderen (1973) reported that feeding low levels of FireMaster BP-6, a fire retardant consisting primarily of polybrominated biphenyls (PBBs) induced lymphoid depletion in the bursa and spleens of chickens and thymic cortex of guinea pigs. Additionally, marked depletion of splenic follicles and periarteriolar lymphocyte sheaths as well as a depressed antibody response following immunization with tetanus toxoid occurred in guinea pigs. Increased interest in PBBs with regard to its affect on the immune system occurred following an accident in 1973 when FireMaster BP-6 was inadvertently substituted for Nutrimaster (a magnesium oxide food supplement for livestock) in the state of Michigan (Dunkel, 1975). An acute lethal toxic syndrome was reported in a working herd inadvertently exposed to PBB-contaminated feed (Mercer et al., 1975). Subsequently, the acute syndrome reoccurred when the offending feed was given to young dairy cattle (Jackson and Halbert, 1974) as well as laboratory animals given PBB orally but only at relatively high dosage levels (Sleight and Sanger, 1976). Clinical observations in working herds suggested that frequent and/or prolonged infection was often present. Chronic disease in cattle following low-level PBB exposure has not been observed in controlled studies, although thymus atrophy has been noted (Jackson and Halbert, 1974). These observations are at least suggestive of a compromised immune system. Furthermore, in a recent study in which 15 calves from a single farm in Michigan were examined, decreased thymic weights and histologic evidence of lymphoid hyperplasia in peripheral lymphoid organs were present (Robinson, 1978). While thymic atrophy can be considered non-specific since many toxic compounds or stressful events may induce similar pathology, it may be indicative of an impairment in the immune response. Immunological test conducted in these cattle revealed only a slight alteration in immune status as evidenced by minimally enhanced lymphoproliferative responses to mitogens and serum IgA concentrations while in general the immunological alterations were unremarkable and may be indicative of low-level exposure or stress (Luster, unpublished). Kately and Bazzell (1978) conducted extensive immunological evaluation in cattle obtained from working herds in Michigan exposed to PBB (up to 30 mg/kg found in fat). Immune alterations were not evident in these cattle as indicated by normal lymphoproliferative responses, antibody production, delayed hypersensitivity reactions and lymphocyte surface markers. Furthermore, the contaminated cattle were not predisposed to autoantibody production or leucotoxic serum factors. It should be noted that calves and cattle from both these studies were obtained from working herds and the length and degree of exposure were unknown.

Shortly after the accident, meat and dairy products containing PBB were widely consumed in the state and subsequently found in the serum and/or adipose tissues of many dairy farmers and local Michigan residents (Humphrey et al., 1975). Bekesi et al. (1978) reported that a high percentage of Michigan dairy farm residents had abnormalities in a number of immune parameters tested (Table 8.5). Alterations included a decrease in peripheral T and B cells as determined by erythrocyte-rosette techniques and an increased number of peripheral lymphocytes without detectable membrane markers. In addition, lymphoproliferative responses were depressed in many Michigan dairy farm residents following stimulation with either phytohemagglutinin, pokeweed mitogen or allogenic leukocytes. Although PBB plasma concentrations did not correlate with depressed immune responses in these subjects, it is well established that PBB plasma levels bear no constant relationship to fat or other tissue PBB concentrations in humans or animals (Carter, 1976; Humphrey et al., 1975). Silva et al. (1979) were unable to confirm these findings as indicated by normal T and B lymphocyte numbers and lymphoproliferative responses to mitogens in individuals previously reported to have either high or low exposure to PBB. It

TABLE 8.5
Mixed leukocyte culture (MLC) reactions and membrane markers from peripheral blood lymphocytes in PBB-exposed Michigan dairy farm residents[a] (Adapted from Bekesi et al., 1978).

Subjects	N	Total No. mononuclear cells ($\times 10^3$/mm^3)	MLC (cpm $\times 10^3$)	E rosettes		EAC rosettes		Lymphocyte with no detectable membrane markers	
				%	Absolute No.	%	Absolute No.	%	Absolute No.
Normal subjects (New York)	79	2.6 ± 0.4	n.d.	74 ± 2	1986 ± 251	22 ± 1	521 ± 52	3.5 ± 0.1	82 ± 15
Wisconsin dairy farm residents	46	2.1 ± 0.1	38.2 ± 1.2	71 ± 2	1473 ± 63	23 ± 1	487 ± 29	6.8 ± 0.5	143 ± 11
PBB-exposed Michigan dairy farm residents									
(with normal lymphoblastogenesis)	27	2.2 ± 0.2	28.2 ± 2.1[d]	60 ± 2[b]	1341 ± 79	21 ± 1	467 ± 34	18.6 ± 1.2[c]	406 ± 32[c]
(with abnormal lymphoblastogenesis)	18	2.1 ± 0.2	10.1 ± 0.3[d]	44 ± 4[d]	917 ± 119[b]	16 ± 1[b]	331 ± 32[b]	40.5 ± 3.9[d]	850 ± 56[d]

a. Mean values ± S.E.
b. $P \leq 0.01$ between Michigan farm residents and Wisconsin farm residents.
c. $P \leq 0.001$ between Michigan farm residents and Wisconsin farm residents.
d. $P \leq 0.00001$ between Michigan farm residents and Wisconsin farm residents.

should be noted, however, that more than a year had elapsed between testing in these two experiments (see also Chapter 9A).

A number of studies have examined PBB-associated affects in laboratory animals. Farber et al. (1978) fed PBB to dogs for 61 days at dosages ranging from 0.06 to 4.0 mg/kg per day. The reported immunopathological alterations were primarily associated with the 4.0 mg/kg dosage group and to a much lesser extent in the 1.0 mg/kg group (dosages that induced overt signs of toxicity). Primary findings in the higher dosage group included reduced hematopoiesis in the bone marrow, a variable degree of lymphocyte depletion in the T cell area of lymph nodes as well as the white pulp of the spleen, and a reduction in IgG-containing lymphocytes in popliteal lymph nodes. Although thymic atrophy was present in all groups to a variable extent, there was no effect on the sheep red blood cell hemagglutination titer or sensitivity to tuberculin. A preliminary report in abstract form, has indicated that alterations may occur in both B and T cell functions in rhesus monkeys after feeding PBB at levels of 1.5 mg/kg for 5 months and 25 mg/kg for 10 weeks (Allen and Lambrecht, 1978). It has been reported that White Leghorn cockerel chicks chronically fed PBB had depressed splenic bursa and thymic weights (Ringer, 1978).

A number of investigators have studied immunological alteration following PBB exposure in rodents. PBB administered orally in mice and rats for 30 days (total of 22 doses) at levels ranging from 0.03 to 30 mg/kg per day caused a reduction in thymic weights of rats and splenic weights of mice (Luster et al., 1978). Furthermore, lymphoproliferative responses following stimulation with T cell mitogens were depressed in the highest dosage group in both species and to a lesser extent in the next highest dosage group (3.0 mg/kg), indicating a dose response. Alterations in humoral-mediated immunity occurred only in mice at the 30 mg/kg dosage level as evidenced by decreases in LPS mitogenic response of splenic lymphocytes, serum immunoglobulin concentrations and antibody responses to SRBCs (PFC/10^6 spleen cells). Wilson et al. (1979) reported depressed antibody responses following acute exposure (167 mg/kg diet for 3 weeks) with respect to both PFCs/10^6 cells as well as total spleen cell yields. After 6 weeks of feeding, however, the PFC/10^6 cells returned to normal values, possibly indicating immunological recovery. Further studies showed the mean survival time of mice fed a diet containing 167 mg PBB/kg for 3 weeks was not effected by *Plasmodium berghei* infection (Mudzinski et al., 1979). Fraker and Aust (1979) reported that PFC responses to SRBCs in mice fed diets containing 1, 10 and 100 mg/kg for 30 days were 80%, 30% and 12%, resp. of control values, although it was not reported whether this was due to PFCs/10^6 cells or total cell yields. Delayed hypersensitivity responses were not effected by this exposure regimen. Recently, Luster et al. (1979a) evaluated immune function following low level chronic exposure (6 months) in mice and rats at dosages ranging from 0.1 to 10.0 mg/kg body weight per day as well as pre/postnatal exposure in mice via maternal dosing. In chronically exposed rats, depressed immune functions were evident in the highest dosage group and included decreased antibody responses to bovine γ-globulin, delayed hypersensitivity responses, and lymphoproliferative responses following stimulation with mitogens or allogenic cells. Cell-mediated immune correlates were affected at lower dosage levels but only where other toxicity was noted, including decreased body weights and severe liver lesions. The immunological system of mice was less affected than rats since immune alterations only occurred in the 10.0 mg/kg dosage group and included decreases in lymphoproliferative responses, serum immunoglobulin levels and resistance to *Listeria monocytogenes* infection. Normal percentages of circulating lymphocytes with B and T cell markers, delayed hypersensitivity responses, PFC responses and bone marrow progenitor cell proliferation occurred in mice at all dosage groups.

Furthermore, immunological alterations were not observed in mice given PBB during pre- and postnatal life through maternal exposure, suggesting that the immune system is not particularly sensitive to PBB during immune ontogeny as appears to be the case with some other environmental chemicals. Parameters examined included delayed-type hypersensitivity responses, lymphoproliferative responses, antibody production, serum immunoglobulin levels, bone marrow progenitor cell proliferation and phagocytosis by macrophages. However, a slight increased sensitivity to endotoxin in pre/postnatally exposed mice was noted although this did not occur in chronically exposed mice. Earlier, Mudzinski et al. (1979) reported a 5-fold increase in endotoxin sensitivity in mice given a diet containing 167 mg/kg for 3 weeks, although this appeared to diminish following feeding the same level for 6 weeks. These studies may be of particular interest since the primary pathway for endotoxin detoxification to be a macrophage-dependent process (Braude et al., 1955) and 1.3% by weight of FireMaster contains silica which is toxic to macrophages (Allison et al., 1966).

8.7 Conclusion

The available data clearly indicate that PCBs may modulate host defense mechanisms and immune responses. The effects of PCBs on humoral immune function appear much clearer than the effects on cell-mediated immune function. PCB exposure consistently suppresses primary and secondary antibody responses, memory cell function and, somewhat less consistently, serum immunoglobulin levels. The effects of PCBs on cell-mediated immune function are somewhat analogous and may reflect alterations of cells which regulate T effector cell function. Delayed hypersensitivity reactions have been observed to be suppressed by PCB exposure while other parameters of cell-mediated immune function, such as graft-vs.-host activity, mixed lymphocyte cultures and in vitro response to mitogens appear somewhat enhanced by PCB exposure. Macrophage functions as determined by in vivo bacterial clearance are inhibited by PCB exposure. The observed increased susceptibility to endotoxin shock may also point to an impaired macrophage function.

TCDD induced thymic atrophy and immunosuppression has been reported to occur in most laboratory animals examined but not as yet in humans. Exposure during pre- and/or postnatal life results in more severe effects than if the chemical is administered during adult life and in some species may be a prerequisite for immunosuppression. The effects appear to be focused on T cell functions although T helper cell function, at least in neonatally exposed rats, are unaffected. Humoral immunity is also compromised in most species but requires higher dosage levels than that which effects cell-mediated immunity. Effects on classical macrophage functions have not been observed. Using conventional immunological procedures, the immunological alterations are usually accompanied by signs of clinical toxicity, particularly decreased body weight gains. Surprisingly, decreased resistance to bacterial infection may occur following low-level exposure without concomitant suppression of functional immune assays or clinical signs of toxicity at least in mice. Increased endotoxin sensitivity has been observed following exposure in mice and may play a role in the decreased resistance following infection with *Salmonella*.

The mechanism(s) of TCDD-induced immunosuppression may be mediated through the cytosolic TCDD receptor. Suppression does not occur through an indirect factor such as undernutrition, altered hormone levels, zinc deficiency, α-fetoprotein or generation of suppressor cells. Evidence now exists that sublethal doses of TCDD can effect bone marrow progenitor cells (possibly lymphocyte stem cells). TCDD can also effect mature lymphocytes directly following in vitro exposure. However, many immunosuppressive drugs are toxic to lymphocytes in vitro at relatively high concentrations and the results have been difficult to correlate with in vivo findings.

The information on the immune effects of TCDF are limited to one study in guinea pigs. This study suggests that the effects of TCDF exposure on the immune system are similar to those reported for TCDD in adult guinea pigs. However, the effects caused by TCDF via this dosage regimen were by no means dramatic since significant effects occurred only at dosage levels approaching levels which induced overt toxicity. In this regard, earlier studies in adult guinea pigs exposed to TCDD through a similar dosage regimen also revealed only modest immunosuppressive effects. It was not until TCDD was administered during the developmental phase of the immune system that the severe consequences of TCDD on the immune system were recognized.

The variety of dosage regimens and the numerous animal species used in studies of PBB-induced immune alterations tend to minimize the validity of any conclusions. Nonetheless, it appears that PBB, while suppressive, is not a particularly potent immunosuppressive chemical, at least in rodents, since immune alterations in these species usually appear at dosage levels where toxic indicators are present such as severe liver lesions and decreased body weight gains. Furthermore, thymic and splenic atrophy is a common but not universal observation. The potential for suppression may be species variable since rats appear more sensitive to the immune effects than mice. The immunological alterations observed in Michigan residents contaminated by PBBs may be indicative of this observation, although the exposure levels in these subjects are as yet unknown. It appears necessary at this time that immunological studies be performed in non-human primates exposed under laboratory conditions to determine if there is a potential for immunosuppression at dosage levels approximating those theoretically determined to have occurred in the Michigan population. The primate studies by Allen and Lambrecht (1978) appear to have been designed to answer these questions.

Evidence also suggests that acute vs. chronic exposure may induce differential effects on the immune system. Splenic weights have been reported decreased following acute exposure (Luster et al., 1978; Wilson et al., 1979) and increased after chronic exposure (Gupta and Moore, 1979), and may indicate recovery. While acute PBB exposure may primarily effect humoral mediated immunity, chronic exposure appears to focus on cell-mediated immunity and in this sense, is not unlike acute vs. low level chronic cyclophosphamide exposure (reviewed by Bach, 1975). This may be interpreted as indicating that PBBs preferentially affect those cells undergoing increased proliferation since B cells are normally more proliferative than T cells. On the other hand, low-level chronic exposure would affect T cells as much if not more than B cells because of their slower renewal.

The severe PBB-induced liver lesions that precede observations of immune dysfunction in rodents may be more than coincidental. Since the primary metabolism of PBB probably occurs at the level of liver microsomal enzymes (Babish et al., 1975), quantitative and/or qualitative changes in PBB metabolism, may be required for immune suppression to occur. This may result directly through PBB or a metabolite acting on immunocompetent and/or precursor cells following liver saturation or indirectly through alteration of steroid metabolism, indicating a PBB–steroid interaction or antagonism. In this respect phenobarbital, a typical microsomal inducer, is an immunosuppressive antagonist when given in conjunction with some weak immunosuppressive drugs (Spreafico et al., 1974).

The various immune studies with PCBs and PBBs were all carried out with mixtures of which the individual compounds will differ in their immunotoxicity potency. In this respect the study of McKinney et al. (1976) is interesting. These authors compared the toxicity of five hexachlorobiphenyl congeners in chickens: 2,3,6,2′,3′,6′-, 2,4,6,2′,4′,6′-, 2,4,5,2′,4′,5′-, 2,3,4,2′,3′,4′- and 3,4,5,3′,4′,5′-. The latter chemical was the most toxic and was the only one to produce thymus atrophy and edema in the chicken; toxic responses similar to those found with TCDD. As reported by Poland et al. (1979), of a series of 16 halogenated biphenyl congeners, only three (3,4,3′,4′-tetrachloro-, 3,4,5,3′,4′,5′-hexachloro- and 3,4,5,3′,4′,5′-hexabromo-; which are stereoisomers of TCDD), induced hepatic aryl hydrocarbon hydroxylase activity. One of these compounds (3,4,5,3′,4′,5′-hexachlorobiphenyl) has been shown to depress parameters of the cell-mediated immunity in young rats after perinatal maternal exposure (Vos et al., unpublished data) and in adult guinea pigs (Luster et al., unpublished data), mimicking the immune effects of TCDD. As PCBs can be contaminated with chlorinated dibenzofurans (Vos et al., 1970), it can be concluded that the immune effects of halogenated biphenyls will largely depend on the presence in the mixture of those compounds that are stereoisomers of TCDD.

The mechanisms by which halogenated biphenyls alter immune function are presently not known. There are at least three basic mechanisms by which these chemicals may alter immune function. These include chemical induced alteration in normal hormone levels which indirectly can alter immune function, chemically induced functional defects of cells involved in the immune response and chemically induced alterations in numbers of responding cell types. Indirect effects of chemicals on the immune system mediated through hormones is certainly possible as various hormones are known to affect immune functions. Chemically induced functional defects in lymphoid tissues could result in a defect in recognition phenomena by lymphoid cells, defects in cellular activation processes or induction of suppressor cells. Depletion of responding cell types as a result of chemical exposure could be due to direct lymphocytotoxicity resulting in death of lymphocytes, blockage of the maturational sequence of specific lymphocyte population development at some point in this sequence, and direct chemical interference with lymphocyte function. The likelihood is that most chemically induced modulation of immune responses is a complex process and involves more than one of the above potential mechanisms of immune suppression.

References

Allen, J.R. and Lambrecht, L. (1978) Responses of rhesus monkeys to polybrominated biphenyls. Toxicol. Appl. Pharmacol. 45, 340–341.

Allison, A.C., Harington, J.S. and Birbeck, M. (1966) An examination of the cytotoxic effects of silica on macrophages. J. Exp. Med. 124, 141–154.

Asherson, G.L. and Zembala, M. (1976) Suppressor T cells in cell-mediated immunity. Br. Med. Bull. 32, 158–164.

Babish, J.G., Gutenmann, W.H. and Sloewand, G.S. (1975) Polybrominated biphenyls: Tissue distribution and effects on hepatic microsomal enzymes in Japanese quail. J. Agr. Food Chem. 23, 879–882.

Bach, J.F. (1975) Corticosteroids. In: Neuberger, A. and Tatum, E.L. (Eds.), The Mode of Action of Immunosuppressive Agents, North-Holland Publishing Co., Amsterdam, pp. 21–91.

Bekesi, J.G., Holland, J.F., Anderson, H.A., Fischbein, A.S., Rom, W., Wolff, M.S. and Selikoff, I.J. (1978) Lymphocyte function of Michigan dairy farmers exposed to polybrominated biphenyls. Science 199, 1207–1209.

Braude, A.I., Carey, F.J. and Zalesky, M. (1955) Studies with radioactive endotoxin. J. Clin. Invest. 34, 858–866.

Bonnyns, M. and Bastomsky, C.H. (1976) Polychlorinated biphenyl induced modification of lymphocyte response to plant mitogens in rats. Experientia 32, 522–523.

Carlstedt-Duke, J.M.B. (1979) Tissue distribution of the receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Cancer Res. 39, 3172–3176.

Carter, L.J. (1976) Michigan's PBB incident: Chemical mixup leads to disaster. Science 192, 240.

Conradt, P., Muller, W.F., Loose, L., Klein, W., Coulston, F. and Korte, F. (1979) Incorporation of (^{3}H) uridine into RNA under the influence of dieldrin and polychlorinated biphenyls. Ecotoxicol. Environ. Safety 3, 10–17.

Dunckel, A.E. (1975) An updating on the polybrominated biphenyl disaster in Michigan. J. Am. Vet. Med. Assoc. 167, 838–843.

Faith, R.E. and Luster, M.I. (1979) Investigations on the effects of 2,3,7,8-TCDD on parameters of various immune functions. Ann. N.Y. Acad. Sci. 320, 564–571.

Faith, R.E. and Moore, J.A. (1977) Impairment of thymus-dependent immune functions by exposure of the developing immune system to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). J. Toxicol. Environ. Health 3, 451–464.

Faith, R.E., Luster, M.I. and Moore, J.A. (1978) Chemical separation of helper cell function and delayed hypersensitivity responses. Cell. Immunol. 40, 275–284.

Faith, R.E., Luster, M.I. and Vos, J.G. (1980) Effects on immunocompetence by chemicals of environmental concern. In: Hodgson, E., Bend, J.R. and Philpot, R.M. (Eds.), Reviews in Biochemical Toxicology, Vol. 2. Elsevier North-Holland, New York, pp. 173–211.

Farber, T., Kasza, L., Giovetti, A., Carter, C., Earl, F. and Balzas, T. (1978) Effect of polybrominated biphenyls (FireMaster BP-6) on the immunological system of the beagle dog. Toxicol. Appl. Pharmacol. 45, 343.

Flick, D.F., O'Dell, R.G. and Childs, V.A. (1965) Studies of the chick edema disease. 3. Similarity of symptoms produced by feeding chlorinated biphenyl. Poultr. Sci. 44, 1460–1465.

Fraker, P.J. and Aust, S. (1979) The antibody and delayed type hypersensitivity response of mice fed polybrominated biphenyls. Toxicol. Appl. Pharmacol. 49, A87.

Friend, M. and Trainer, D.O. (1970) Polychlorinated biphenyl: Interaction with duck hepatitis virus. Science 170, 1314–1316.

Godeberg, O.V., Rhodes, J.M. and Larsen, S.O. (1975) The effect of various immunosuppressive agents on mouse peritoneal macrophages and on the in vitro phagocytosis of Escherichia coli 04:K3:H5 and degradation of ^{125}I-labelled HSA–antibody complexes by these cells. Immunology 28, 59–70.

Gontzea, I. (1974) Nutrition and Anti-infectious Defense. S. Karger, Basel.

Greaves, M.F., Owen, J.J.T. and Raff, M.C. (1973) T and B Lymphocytes: Origins, Properties and Roles in Immune Responses. Excerpta Medica, Amsterdam.

Gupta, B.N., Vos, J.G., Moore, J.A., Zinkl, J.G. and Bullock, B.C. (1973) Pathologic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals. Environ. Health Perspect. 5, 125–140.

Gupta, B.N. and Moore, J.A. (1979) Toxicologic assessments of a commercial polybrominated biphenyl mixture in the rat. Am. J. Vet. Res. 40, 1458–1468.

Hinsdill, R.D., Thomas, P.T. and Couch, D. (1980) Immunotoxicity assessment of dioxins. In: Proceedings of the Fourth FDA Science Symposium: Inadvertent Modification of the Immune Response. The Effects of Foods, Drugs and Environmental Contaminants. Office of Health Affairs, Food and Drug Administration, Rockville, Md., pp. 76–79.

Humphrey, J.H. and White, R.G. (1970) Immunology for Students of Medicine, 3rd Edn., Blackwell Scientific Publications, Oxford.

Humphrey, H.E.B., Haynes, N.S. and Budd, M.L. (1975) PBB analysis in dairy farmers and residents of the State of Michigan. In: Hemphill, D.D. (Ed.), Trace Substances in Environmental Health IX, University of Missouri Press, Columbia.

Jackson, T.F. and Halbert, F.L. (1974) A toxic syndrome associated with the feeding of polybrominated biphenyl-contaminated protein concentrate to dairy cattle. J. Am. Vet. Med. Assoc. 165, 437–439.

Kateley, J.R. and Bazzeil, S.J. (1978) Immunological studies in cattle exposed to polybrominated biphenyls. Environ. Health Persp. 23, 75–82.

Kerkvliet, N.I. and Kimeldorf, D.J. (1977) Antitumor activity of a polychlorinated biphenyl mixture, Aroclor 1254, in rats inoculated with Walker 256 carcinosarcoma cells. J. Natl. Cancer Inst. 59, 951–955.

Koller, L.D. (1977) Enhanced polychlorinated biphenyl lesions in Moloney leukemia virus-infected mice. Clin. Toxicol. 11, 107–116.

Koller, L.D. and Thigpen, J.E. (1973) Reduction of antibody to pseudorabies virus in polychlorinated biphenyl-exposed rabbits. Am. J. Vet. Res. 34, 1605–1606.

Kouri, R.E., Ratrie, H., III, Atlas, S.A., Niwa, A. and Nebert, D.W. (1975) Aryl hydrocarbon hydroxylase induction in human lymphocytes cultures by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Life Sci. 15, 1585–1595.

Langevoort, H.L., Cohn, Z.A., Hirsch, J.G., Humphrey, J.H., Spector, W.G. and van Furth, R. (1970) The nomenclature of mononuclear phagocytic cells. Proposal for a new classification. In: van Furth, R. (Ed.), Mononuclear Phagocytes, Blackwell Scientific Publications, Oxford, pp. 1–6.

Loose, L.D., Pittman, K.A., Benitz, K.F. and Silkworth, J.B. (1977) Polychlorinated biphenyl and hexachlorobenzene induced humoral immunosuppression. J. Reticuloendo. Soc. 22, 253–271.

Loose, L.D., Silkworth, J.B., Pittman, K.A., Benitz, K.F. and Mueller, W. (1978) Impaired host resistance to endotoxin and malaria in polychlorinated biphenyl- and hexachlorobenzene-treated mice. Infect. Immun. 20, 30–35.

Luster, M.I., Faith, R.E. and Moore, J.A. (1978) Effects of polybrominated biphenyls (PBB) on immune response in rodents. Environ. Health Persp. 23, 227–232.

Luster, M.I., Boorman, G.A., Harris, M.W. and Moore, J.A. (1979a) Laboratory studies on polybrominated biphenyl induced immune alterations following low-level chronic or pre/postnatal exposure. Int. J. Immunopharmacol., in press.

Luster, M.I., Clark, G., Lawson, L.D. and Faith, R.E. (1979b) Effects of brief in vitro exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on mouse lymphocytes. J. Environ. Pathol. Toxicol. 2, 965–977.

Luster, M.I., Faith, R.E. and Clark, G. (1979c) Laboratory studies on the immune effects of halogenated aromatics. Ann. N.Y. Acad. Sci. 320, 473–486.

Luster, M.I., Faith, R.E. and Lawson, L.D. (1979d) Effects of 2,3,7,8-tetrachlorodibenzofuran (TCDF) on the immune system in guinea pigs. Drug Chem. Toxicol. 2, 49–60.

Luster, M.I., Boorman, G.A., Harris, M.W., Luebke, R.W., Thigpen, J.E., Padarathsingh, M.L. and Moore, J.A. (1980) The effect on bone marrow, immunological parameters and host susceptibility caused by pre- and postnatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Int. J. Immunopharmacol., in press.

Matsumura, F. and Benezet, H.J. (1973) Studies on the bioaccumulation and microbial degradation of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ. Health Perspect. 5, 253–258.

McConnell, E.E., Moore, J.A., Haseman, J.K. and Harris, M.W. (1978) The comparative toxicity of chlorinated dibenzo-p-dioxins in mice and guinea pigs. Toxicol. Appl. Pharmacol. 44, 335–356.

McKinney, J.D., Chae, K., Gupta, B.N., Moore, J.A. and Goldstein, J.A. (1976) Toxicological assessment of hexachlorobiphenyl isomers and 2,3,7,8-tetrachlorodibenzofuran in chicks. I. Relationship of chemical parameters. Toxicol. Appl. Pharmacol. 36, 65–80.

Mercer, H., Furr, A., Meeidink, G., Condon, R.J., Buck, W., Teste, R.H. and Fries, G. (1975) Michigan State dairy herd survey. A report on herd health status of animals exposed to polybrominated biphenyls (PBB). Food and Drug Administrations, Beltsville, Md.

Moore, J.A. and Faith, R.E. (1976) Immunologic response and factors affecting its assessment. Environ. Health Persp. 18, 125–131.

Moore, J.A., Gupta, B.N. and Vos, J.G. (1976) Toxicity of 2,3,7,8-tetrachlorodibenzofuran: Preliminary results. Proceedings National Conference on Polychlorinated Biphenyls. Environmental Protection Agency, Office of Toxic Substances, Washington, D.C., pp. 77–80.

Morita, M. and Oishi, S. (1977) Clearance and tissue distribution of polychlorinated dibenzofurans in mice. Bull. Environ. Contam. Toxicol. 18, 61–66.

Mudzinski, S., Silkworth, J.B., Wilson, N.M. and Loose, L.D. (1979) Influence of polybrominated biphenyls on immunological host defense parameters. Toxicol. App. Pharmacol. 49, A87.

Niwa, A., Kumaki, K. and Nebert, D.W. (1975) Induction of aryl hydrocarbon hydroxylase activity in various cell cultures by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Mol. Pharmacol. 11, 399–408.

Pierce, C.W. and Kapp, J.A. (1976) The role of macrophages in antibody responses in vitro. In: Nelson, D.S. (Ed.), Immunobiology of the Macrophage, Academic Press, New York, p. 2.

Poe, W.J. and Michael, J.G. (1976) Separation of the mitogenic and antigenic response to bacterial lipopolysaccharide. Immunology 30, 241–248.

Poland, A. and Glover, E. (1976) Stereospecific, high affinity binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin by hepatic cytosol. J. Biol. Chem. 251, 4936–4945.

Poland, A., Greenlee, W.F. and Kende, A.S. (1979) Studies on the mechanism of action of the chlorinated dibenzo-p-dioxins and related compounds. Ann. N.Y. Acad. Sci. 320, 214–230.

Reggiani, G. (1978) Medical problems raised by the TCDD contamination in Seveso, Italy. Arch. Toxicol. 40, 161–188.

Ringer, R.K. (1978) PBB fed to immature chickens. Its effect on organ weights and function and on the cardiovascular system. Environ. Health Persp. 23, 247–255.

Robinson, F.R. (1978) Biologic response of cattle to low levels of Firemaster FF-1. Presented at the AVMA Meeting, Dallas, Texas, July 1978.

Roitt, I.M. (1974) Essential Immunology, 2nd Edn., Blackwell Scientific Publications, Oxford.

Scrimshaw, N.S., Taylor, C.E. and Gordon, J.E. (1968) Interactions of Nutrition and Infection. WHO Monogr. Ser. No. 57.

Sharma, R.P., Kociba, R.J. and Gehring, P.J. (1978) Immunotoxicologic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals. Toxicol. Appl. Pharmacol. 45, 333.

Silkworth, J.B. and Loose, L.D. (1978) Cell-mediated immunity in mice fed either Aroclor 1016 or hexachlorobenzene. Toxicol. Appl. Pharmacol. 45, 326–327.

Silkworth, J.B. and Loose, L.D. (1979) PCB and HCB induced alteration of lymphocyte blastogenesis. Toxicol. Appl. Pharmacol. 49, A86.

Silva, J., Kauffman, C.A., Simon, D.G., Landrigan, P.J., Humphrey, H.E.B., Heath, C.W., Wilcox, K.R., Van Amburg, G., Kaslow, R.A., Ringel, A. and Hoff, K. (1979) Lymphocyte function in humans exposed to polybrominated biphenyls. J. Retic. Soc. 26, 341–347.

Sleight, S.C. and Sanger, V.L. (1976) Pathological features of polybrominated biphenyl toxicosis in the rat and guinea pig. J. Am. Vet. Med. Assoc. 169, 1231–1235.

Smith, S.H., Sanders, V.M., Barrett, B.A., Borzellera, J.F. and Munson, A.E. (1978) Immunotoxicological evaluation on mice exposed to polychlorinated biphenyls. Toxicol. Appl. Pharmacol. 45, 330.

Spreafico, F. and Anaclerio, A. (1977) Immunosuppressive agents. In: Hadden, J.W., Coffey, R.G. and Spreafico, F. (Eds.), Comprehensive Immunology 3, Plenum Publishing Co., New York, pp. 245–278.

Spreafico, F., Donelli, M.G., Vecchi, A., Bossi, A. and Garattini, S. (1974) In: Mathe, G. and Oldham, R.K. (Eds.), Recent Results in Cancer Research, Vol. 49, Springer-Verlag, Berlin, pp. 88–109.

Street, J.C. and Sharma, R.P. (1975) Alteration of induced cellular and humoral immune responses by pesticides and chemicals of environmental concern: Quantitative studies of immunosuppression by DDT, Aroclor 1254, Carbaryl, Carbofuran and methylparathion. Toxicol. Appl. Pharmacol. 32, 587–602.

Taylor, R.B. and Basten, A. (1976) Suppressor cells in humoral immunity and tolerance. Br. Med. Bull. 32, 152–157.

Thigpen, J.E., Faith, R.E., McConnell, E.E. and Moore, J.A. (1975) Increased susceptibility to bacterial infection as a sequela of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Infection Immun. 12, 1319–1324.

Thomas, P.T. and Hinsdill, R.O. (1978) Effect of polychlorinated biphenyls on the immune responses of rhesus monkeys and mice. Toxicol. Appl. Pharmacol. 44, 41–51.

Thomas, P.T. and Hinsdill, R.D. (1979) The effect of perinatal exposure to tetrachlorodibenzo-p-dioxin on the immune response of young mice. Drug Chem. Toxicol. 2, 77–98.

Turk, J.L., Polak, L. and Parker, D. (1976) Control mechanisms in delayed-type hypersensitivity. Br. Med. Bull. 32, 165–170.

Van Logten, M.J., Gupta, B.N., McConnell, E.E. and Moore, J.A. (1980) Role of the endocrine system in the action of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the thymus. Toxicology 15, 135–144.

Van Logten, M.J., Gupta, B.N., McConnell, E.E. and Moore, J.A. The influence of malnutrition on the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats, in preparation.

Van Miller, J.P., Marlar, R.J. and Allen, J.R. (1976) Tissue distribution and excretion of tritiated tetrachlorodibenzo-p-dioxin in non-human primates and rats. Food Cosmet. Toxicol. 14, 31–34.

Vos, J.G. (1977) Immune suppression as related to toxicology. CRC Crit. Rev. Toxicol. 5, 67–101.

Vos, J.G. (1978) 2,3,7,8-Tetrachlorodibenzo-p-dioxin: effects and mechanisms. Ecol. Bull. (Stockholm) 27, 165–176.

Vos, J.G. and Beems, R.B. (1971) Dermal toxicity studies of technical polychlorinated biphenyls and fractions thereof in rabbits. Toxicol. Appl. Pharmacol. 19, 617–633.

Vos, J.G. and van Driel Grootenhuis, L. (1972) PCB-induced suppression of the humoral and cell-mediated immunity in guinea pigs. Sci. Total Environ. 1, 289–302.

Vos, J.G. and van Genderen, H. (1973) Toxicological aspects of immunosuppression. In: Deichmann, W.B. (Ed.) Pesticides and the Environment: A Continuing Controversy, Intercontinental Medical Book Corp., New York, pp. 527–545.

Vos, J.G. and Koeman, J.H. (1970) Comparative toxicologic study with polychlorinated biphenyls in chickens with special reference to porphyria, edema formation, liver necrosis, and tissue residues. Toxicol. Appl. Pharmacol. 17, 656–668.

Vos, J.G. and de Roij, Th. (1972) Immunosuppressive activity of a polychlorinated biphenyl preparation on the humoral immune response in guinea pigs. Toxicol. Appl. Pharmacol. 21, 549–555.

Vos, J.G., Koeman, J.H., van der Maas, H.L., ten Noever de Brauw, M.C. and de Vos, R.H. (1970) Identification and toxicological evaluation of chlorinated dibenzofuran and chlorinated naphthalene in two commercial polychlorinated biphenyls. Food Cosmet. Toxicol. 8, 625–633.

Vos, J.G., Moore, J.A. and Zinkl, J.G. (1973) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the immune system of laboratory animals. Environ. Health Persp. 5, 149–162.

Vos, J.G. and Moore, J.A. (1974) Suppression of cellular immunity in rats and mice by maternal treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Int. Arch. Allergy Appl. Immunol. 47, 777–794.

Vos, J.G., Kreeftenberg, J.G., Engel, H.W.B., Minderhoud, A. and van Noorle Jansen, L.M. (1978) Studies on 2,3,7,8-tetrachlorodibenzo-p-dioxin induced immune suppression and decreased resistance to infection: endotoxin hypersensitivity, serum zinc concentrations and effect of thymosin treatment. Toxicology 9, 75–86.

Weissberg, J.G. and Zinkl, J.G. (1973) Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin upon hemostasis and hematologic function in the rat. Environ. Health Persp. 5, 119–123.

White, A. and Goldstein, A.L. (1972) Hormonal regulation of host immunity. In: Borek, F.

(Ed.), Immunogenicity, Frontiers of Biology, Vol. 25, North-Holland Publishing Co., Amsterdam, pp. 334–364.

Wilson, N., Mudzinski, S., Silkworth, J. and Loose, L.D. (1979) Influence of polybrominated biphenyl on the splenic antibody response in the mouse. Toxicol. Appl. Pharmacol. 49, A89.

Zinkl, J.G., Vos, J.G., Moore, J.A. and Gupta, B.N. (1973) Hematologic and clinical chemistry effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals. Environ. Health Persp. 5, 111–118.

PORPHYRIA CUTANEA TARDA

Karl E. Anderson, M.D.
Associate Professor and Physician
The Rockefeller University Hospital
1230 York Avenue
New York, N.Y. 10021

Prepared for the Subcommittee on Compensation,
Pension and Insurance
Committee on Veterans Affairs
U.S. House of Representatives
335 Cannon House Office Building
Washington, D.C. 20515

July 8, 1983

Introduction:

The porphyrias are a group of disorders which are due to specific metabolic defects in the body. Porphyria cutanea tarda (PCT) is the most common of the porphyrias. Both acquired and genetic forms of PCT occur in the general population. In addition there have been a few outbreaks reported from TCDD exposure. PCT can be associated with skin changes and mild or moderate liver damage. Neurological effects occur in certain other types of porphyria but do not develop as a result of PCT. A deficiency of the same enzyme is found in both acquired and genetic forms of PCT, and additional factors such as iron, alcohol, and estrogens can contribute to both.

Prevalence:

The prevalence of PCT has not been accurately estimated in most localities. Although it is the most common of the porphyrias, it is still an uncommon disease. It appears more common in countries in which alcohol consumption is high, such as in many Western countries and among the Bantu population in South Africa. For example, almost 700 cases were known in 1974 in Prague, Czechoslovakia, alone. PCT has been more common in men, perhaps due to greater alcohol intake. More recently the relative frequency of female patients has been increasing due in part to oral contraceptive use, post-menopausal estrogen treatment, and alcohol ingestion. The disease usually occurs in late adult life but onset at younger ages is now more common than in the past. PCT rarely occurs in children, and if it does it is very likely to be genetic. Other than its relation to liver disease, PCT occurs also in association with diabetes mellitus, systemic or discoid lupus erythrematosus, other immunological disorders, and in uremic patients undergoing hemodialysis more frequently than would be expected by chance.

Clinical Features:

The chief symptom of PCT is photosensitivity of the skin. This occurs on sun-exposed areas and is manifested by blisters which can be large and painful and by increased fragility of the skin. Scarring and secondary infection can result from these blisters. How excess porphyrins found in these patients can produce skin damage is not fully understood, but it is generally held that porphyrins absorb energy from ultraviolet light and then release that energy in a form that is damaging to the skin. PCT is generally successfully treated and does not result in long-term disability.

The Metabolic Defect in PCT:

The specific metabolic defect associated with PCT is a partial deficiency in the liver of an enzyme termed uroporphyrinogen decarboxylase (URO-D). URO-D is one of eight enzymes which comprise the metabolic pathway to make heme in the body from simpler molecules. Several porphyrins are intermediates in the later portion of the synthetic pathway for heme. URO-D carries out a complex transformation of one of the porphyrins (uroporphyrinogen) in the pathway.

Heme is probably made in all cells in the body, but is made in largest amounts in the bone marrow and the liver because these tissues require heme in large amounts. In the bone marrow heme is used primarily to make hemoglobin. Heme in the liver is used to make a group of proteins that require heme as a substituent molecule and are called cytochromes.

When URO-D is deficient, as in PCT, body tissues can still make enough heme, but because of a partial deficiency of URO-D this may occur at the expense of excess porphyrin formation and porphyrin accumulation in the body. In PCT, porphyrins gradually build up in the liver and then spill over into the blood plasma which carries them to the skin. Because porphyrins first accumulate in the liver in PCT and because there is regularly some degree of liver damage, the disease is classified as one of the hepatic porphyrias. The blood plasma also carries excess porphyrins to the kidneys, and porphyrins are then excreted in urine. Some of the excess porphyrins are also secreted in bile by the liver, and these then enter the intestine and appear in feces.

In this manner, URO-D deficiency in the liver results in a characteristic pattern of porphyrin excretion in the urine and feces. This pattern is more complex than can be fully described and explained in this brief presentation. The primary feature of the pattern in urine is excess uroporphyrin and 7-carboxylate porphyrin, and in feces, excess isocoproporphyrin. The latter is a particular hallmark of a deficiency of URO-D in the liver. The porphyrin patterns in urine and feces in PCT patients are so characteristic that their analysis is an important means of diagnosis.

Genetic and Acquired Forms:

Research findings published in approximately the last 10 years have added considerably to our understanding of PCT. It has become clear that in a substantial minority of patients a genetic deficiency of URO-D underlies the disease, and that the same deficiency is found on the average in half of their immediate relatives. The disease is fully manifest in few other family members. In the genetic form of PCT, URO-D is deficient in all cells in the body, even though excess porphyrins probably are produced only in the liver.

Most patients with PCT appear to have a truly sporadic or acquired form of the disease. In these individuals URO-D is deficient only in the liver. Why the liver enzyme becomes deficient in these patients is not known. Thus there are at least two forms of PCT both occurring rather uncommonly in the general population. The clinical manifestations and porphyrin excretion patterns of the genetic and acquired forms are little if at all different. It is possible to distinguish the genetic form of PCT by finding low URO-D in tissues other than the liver - for example red blood cells. Assays for URO-D are difficult and therefore not widely available at the present time.

Research in laboratory animals has also provided important new knowledge, particularly about relationships of PCT to chemical exposures. Certain chlorinated hydrocarbons, including dioxin, can inhibit URO-D in animals and produce a condition resembling PCT. This was first demonstrated with hexachlorobenzene in the late 1950's. A number of chemicals that clearly play a role in human PCT, such as alcohol, iron, and estrogens, do not produce PCT when administered to animals, and do not themselves inhibit URO-D. In animals exposed to chlorinated hydrocarbons, iron administration does enhance the development of porphyria.

Exposure of animals to hexachlorobenzene or a number of other chlorinated cyclic hydrocarbons can produce a porphyria that mimics PCT very closely.

This was shown after a massive outbreak of a PCT-like syndrome occurred in humans in 1956 in eastern Turkey when seed wheat to which hexachlorobenzene had been added as a fungicide was used for food by a large impoverished population. It was estimated that over 3000 persons developed porphyria as a result of this toxic chemical exposure. Photosensitivity with bullae, scarring, hyperpigmentation, and marked hypertrichosis was common. Porphyria in this population was more common in children than in adults, and because of increased hair growth and pigmentation many were described as having "monkey disease." The incidence was slightly greater in males than in females. An average interval of about 6 months was calculated between exposure and the development of symptoms. Early periods of illness were often accompanied by irritability, colic, anorexia, weakness, and red or brown urine. Painless arthritis was especially common in children. Many breast-fed infants in some villages died of a condition known locally as "pink sore" which was characterized by weakness, convulsions, and cutaneous annular erythema, and this illness may have resulted from hexachlorobenzene in breast milk. Older children and adults who developed porphyria and complained of irritability and weakness may have had the neurological involvement that has been observed in hexachlorobenzene-treated animals. Moreover in these animals it is unclear whether weakness results from the induced porphyria or from a direct toxic effect of hexachlorobenzene on the nervous system. Cripps and coworkers reexamined 32 patients with "porphyria turcica" 20 years after the initial illness, and found that although many had sequelae (scarring, increased pigment, hypertrichosis, pinched facies with perioral scarring, short stature, and contracted hands and fingers), porphyrin excretion had returned to normal or nearly normal levels without treatment. This disease originally developed in old Turkish settlers as well as immigrant Turks and Kurds. This is evidence against, but does not exclude, a genetic predisposition.

Smaller outbreaks and isolated cases of PCT from exposure to other cyclic chlorinated hydrocarbons, including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, or dioxin), have also been reported. For example, in 1964, 29 workers at a plant for the manufacture of 2,4,-D and 2,4,5-T in Newark, NJ, were studied for chloracne, and 11 were found to have increased urinary uroporphyrins (by a qualitative test). At least 2 of these 11 workers had skin manifestations consistent with PCT. In Czechoslovakia, 80 out of 400 workers engaged in the production of 2,4,5-T became ill between 1965 and 1968. Fiftyfive consented to medical evaluation, and 11 of those were described as having PCT with skin lesions and increased uroporphyrin in urine (172-2230 μg/24h). The time course of the PCT was not well described, but it seemed to develop quite soon after exposure, and to resolve fairly completely with follow-up over a period of 10 years or longer.

In subjects exposed to TCDD, porphyrin fluorescence in the liver is quite prevalent, even with little or no increase in urine porphyrins. Improved industrial hygiene can substantially reduce the prevalence of PCT and excess urinary uroporphyrin among the workers. Abnormalities in porphyrin metabolism in laboratory animals or cultured liver cells similar to those in hexachlorobenzene porphyria can be produced also by polychlorinated biphenyls (PCB), TCDD, and polybrominated biphenyls (PBB). The possibility is worth considering that inapparent exposure to such industrial and environmental chemicals may predispose to the development of some sporadic cases of PCT that we see in the general population.

The few dioxin-related outbreaks of porphyria that have occurred in humans are not optimally described in the medical literature. Exposed individuals often developed a variety of symptoms probably due to toxic effects of dioxin other than the porphyria. The matters of a latent period and how much disability resulted from the porphyria itself are not specifically addressed in the published reports.

DR. JOHN BEDERKA

DIOXIN-ASSOCIATED ADVERSE HUMAN HEALTH EFFECTS

My purpose for presenting the following information is to add to the growing body of knowledge regarding the health hazard to the human that has been contaminated with Dioxin 2,3,7,8-TCDD and/or Dioxin-containing products such as phenoxyacid herbicides. By way of background to gain an increased perspective, the Dioxin-related animal studies of the last 10-15 years clearly show the broad spectrum toxicity of TCDD. The multiple species that have been used in toxicologic studies have shown Dioxin to be toxic at essentially all levels of the organism. For many tissues, there is some seeming tissue and/or species specificity for special toxicologic pathologic sensitivities such as the thymus and adipose tissue. Excepting for now the multitude of seemingly non-lethal toxicologic manifestations such as generalized enzyme induction, porphyria, etc., I would like to focus upon the life-threatening process of Dioxin-related neoplastic growths; i.e., cancers. At my latest count, Dioxin-treatment has been associated with increased incidences of cancer in the following tissues in diverse animals:

- Blood
- Brain
- Ear
- Kidney
- Liver
- Lung
- Muscle
- Skin
- Testes
- Peritoneum

It is clear from the cellular differentiation scheme that these tissues are of diverse origin in the embryo and are at various stages of differentation when affected. Recent studies have further shown Dioxin to be the most potent co-carcinogen. Thus, when Dioxin is administered along with a known carcinogen, the speed of onset and incidence of cancer are both enhanced.

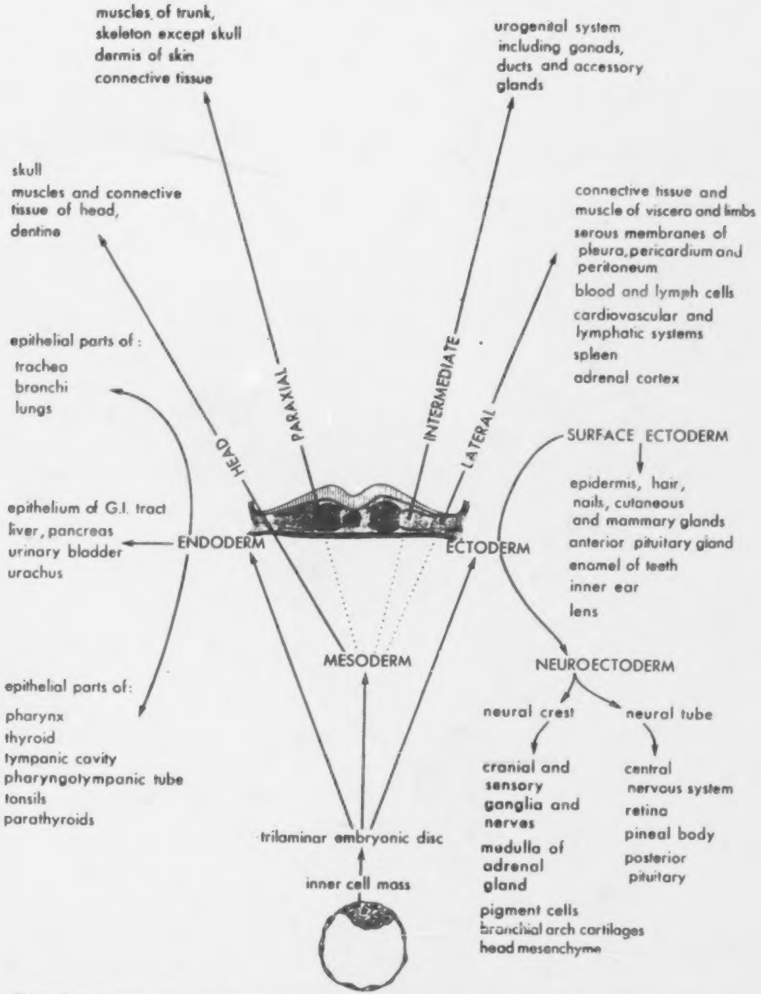
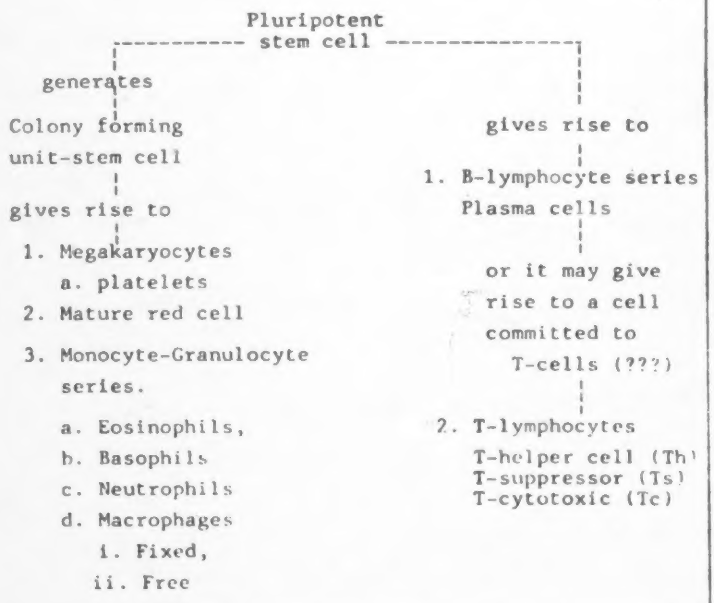

muscles of trunk,
skeleton except skull
dermis of skin
connective tissue
urogenital system
including gonads,
ducts and accessory
glands
skull
muscles and connective
tissue of head,
dentine
connective tissue and
muscle of viscera and limbs
serous membranes of
pleura, pericardium and
peritoneum
blood and lymph cells
cardiovascular and
lymphatic systems
spleen
adrenal cortex
epithelial parts of:
trachea
bronchi
lungs
PARAXIAL
INTERMEDIATE
HEAD
LATERAL
SURFACE ECTODERM
epidermis, hair,
nails, cutaneous
and mammary glands
anterior pituitary gland
enamel of teeth
inner ear
lens
epithelium of G.I. tract
liver, pancreas
urinary bladder
urachus
ENDODERM
ECTODERM
MESODERM
NEUROECTODERM
epithelial parts of:
pharynx
thyroid
tympanic cavity
pharyngotympanic tube
tonsils
parathyroids
neural crest
neural tube
cranial and
sensory
ganglia and
nerves
medulla of
adrenal
gland
pigment cells
branchial arch cartilages
head mesenchyme
central
nervous system
retina
pineal body
posterior
pituitary
trilaminar embryonic disc
inner cell mass

Figure 5–5 Scheme illustrating the origin and derivatives of the three germ layers. The cells of these layers make specific contributions to the formation of the different tissues and organs.

FIGURE III

HEMATOPOIESIS:

COMPOSITE CONTINUUM MODEL


Pluripotent stem cell
generates
Colony forming unit-stem cell
gives rise to
1. Megakaryocytes
a. platelets
2. Mature red cell
3. Monocyte-Granulocyte series.
a. Eosinophils,
b. Basophils
c. Neutrophils
d. Macrophages
i. Fixed,
ii. Free
gives rise to
1. B-lymphocyte series
Plasma cells
or it may give rise to a cell committed to T-cells (???)
2. T-lymphocytes
T-helper cell (Th)
T-suppressor (Ts)
T-cytotoxic (Tc)

Data above prepared from synthesis of information from Botnick et al, 1979; Till and McCulloch 1980; Cline and Golde, 1979; Beck, 1981, by J.Prince, 1983.

More to the point, I would like to now emphasize that there are at least three types of toxic manifestations that are Dioxin-associated in the human. These are:

1. Immunologic dysfunction
2. Chloracne, and
3. Soft Tissue cancers.

I would like to emphasize that these may all be considered as neoplastic in that they involve an apparent mutagenic effect in 1, a dedifferentation in 2, and classic cancers in 3. Furthermore, all three pathologic states apparently persist and/or recur in the apparent absence of the initiating Dioxin or at very low and/or undetectable tissue levels of Dioxin.

In the case of the Dioxin-associated immunologic dysfunction, Joe Prince, with whom I have been associated for about the last four years, and Dr. Ward have recently reported similar findings as shown in the Immunologic Dysfunction tabulation of Scheme 2. With regard to Dioxin-associated Chloracne in the human, the clinical picture is quite clear and has been known since about 1955. The incidence of Chloracne can be as low as 5% in well documented Dioxin-associated exposures and the latency for signs can be as long as about 15 years. The skin lesions are dedifferentiated tissue, thus, neoplastic if not malignant. Furthermore, the Chloracne is not an absolute indicator of additional disease; and the absence of Chloracne in a Dioxin-exposed individual is not indicative of the absence of additional pathology.

Concerning my third point, there are several studies that show an increased incidence of soft tissue cancer in humans with known Dioxin-associated and other chemical exposures. The work of Hardell and associates is premiere in regard to Dioxin and phenoxyacid herbicides. The cancer involved is known as lymphoma. Furthermore, concomitant exposure to other chemicals, some of which are also carcinogenic, was calculated to increase the health risks. Other investigators have found increased incidences of lymphomas in the skin, scalp tumors, frequently associated with prolonged Chloracne as well as other less specific signs and symptoms. Not incidentally, this complex of events including diverse cancers, skin rash, varied signs and symptoms, Dioxin associated phenoxyacid herbicide and other cancer causing chemical exposures is completely consistent with the circumstance of the Viet Nam veteran victim of Agent Orange, Agent White, etc.

In summary, Dioxin-associated adverse human health effects were described as three general clinical conditions: 1) Immunological dysfunction; 2) Chloracne; and 3) Soft tissue cancers. The immune dysfunction appears to be the result of a Dioxin-related mutation and/or chronic toxic effect on a bone-marrow cell. The cells then show abnormal numbers and functions as seemingly mature white blood cells. The abnormal immune function would allow abnormal cell growth and regulation which could be exhibited by increased susceptibility to bacterial and/or viral related diseases and by abnormal growth such as Chloracne and soft tissue cancers. The co-carcinogenic effect of Dioxin and other toxic chemicals, if present in the human, would speed up and intensify the disease processes especially in the more vulnerable individual.

Copy of prepared text of testimony by John P. Bederka, Jr., Ph.D. before the Subcommittee on Compensation, Pension and Insurance in Room 334 CHOB, July 12, 1983 in Re:'Hearing on H.R. 1961, to provide compensation for certain disabilities which may have been caused by exposure to phenoxy herbicides while serving in Southeast Asia during the Vietnam era.

SCHEME 2. IMMUNOLOGIC DYSFUNCTION

1. White blood cell levels were significantly increased.
2. Eosinophil count was elevated significantly.
3. IgM was significantly decreased in part of the most exposed group. Acts on viruses and particulates.
4. IgD was very low in portions of both exposed groups. Involved in T-Cell to B-Cell communication.
5. Bacterial binding data:
   - B1, B2 and Total B-Cells show significantly decreased capabilities.
   - T-2 cells show significantly decreased capabilities.
6. Pokeweed Mitogen stimulation:
   - B-Cells were significantly activated.
7. PHA stimulation: T-Cells stimulation was decreased in a portion of Group C.
8. Neutrophil chemiluminescence was significantly decreased in regard to anti-human IgG biobeads test.
9. Neutrophil ATP levels were significantly decreased.
10. Overall white blood cell parameters were significantly abnormal.